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Acromegaly: A Consideration of Its Course and Treatment

Report of Four Cases with Autopsies

[Pituitary Adenoma]

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IN THE FINAL analysis it is long personal familiarity with, and a critical discriminating attitude toward, a wealth of clinical material that add a modicum of authoritative information to the sum of our knowledge of a given disease. Lack of opportunity to fulfill these requirements probably accounts for the fact that very little has been added to our knowledge of acromegaly since the comprehensive work of Cushing and Davidoff (1–5) was published nearly 15 years ago. Although many of their conclusions were hypothetical at the time, they have since been substantiated in the light of newer knowledge concerning the pituitary gland. Their analysis included 100 verified cases, a truly sizeable series considering the rarity of the disease. Up to 1938, Atkinson (6, 7, 8), after diligent search of the literature and with the aid of the British Consular Service all over the world, had been able to uncover only 1606 cases of acromegaly which he tabulated in a unique monograph. Approximately 55 additional cases which were reported during the past 4 years have brought the total to 1661. Autopsies have been performed in less than one-fourth of these. At the University of California Hospital, over a 5-year period from 1937–1941, 12 cases have been so diagnosed among 35,757 entries, or in incidence of 1 in 3000. This figure is rather different from that reported by the Boston City Hospital for a 6-year period from 1930 to 1935, during which time the diagnosis of acromegaly was made in 14 cases among 210,094 entries, or an incidence of 1 in 15,000.

This bizarre malady is not only rare but it is also impressive in its manifestations, protean in its symptomatology, and kaleidoscopic in its involvement of more tissues and organs than almost any other disease. The onset is likely to be insidious; the course usually is chronic and of long duration and is marked by successive waves of remissions and exacerbations. These characteristics combine to render difficult the clear evaluation of the findings in a single case and, even more so, of the efficacy of any specific form of treatment. One dare not theorize or draw sweeping conclusions from one or two cases. Even the postmortem observations may be misleading unless a correlation has been established between them and the clinical status at the time of death.

In this paper we are reporting the cases of four acromegalics whom we have had the opportunity to follow for an extended period of time and in whom autopsies were performed. Three are from the Out-Patient Department of the University of California Hospital and one is from the Out-Patient Department

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of the Hospital for Women and Children. A review of the histories leaves us dissatisfied with the therapeutic results achieved and convinces us that, in distinction from the neurological aspects, the more pervasive endocrinological derangements of this disease are not receiving the attention they deserve. It seems to us desirable, therefore, to record the course of the disease in these four patients and to discuss what might have been accomplished by earlier and more vigorous therapy.

CASE REPORTS

Case 1 (*U. C. H. No. 1707*). Progressive acromegaly of 17 years' duration in a man, treated by pituitary irradiation in inadequate amounts. Subtotal hypophysectomy, urged in the early stages of the disease to prevent further deformity and the possible development of diabetes mellitus, was refused. Diabetes mellitus developed 6 months prior to death which occurred at age 37 from gas and oxygen anesthesia preparatory to resection of a pilonidal cyst. An enlarged thymus was found at autopsy.

A 23-year-old unmarried student mechanic presented himself at the Out-Patient Department of the University of California Hospital on Dec. 17, 1923, with a complaint of severe frontal headache of 6 months' duration. For at least 3 years he had noticed gradual coarsening of his features, protrusion of the lower jaw, increasing spacing of his teeth with attendant difficulty in chewing and gradual enlargement of his hands both in thickness and in width. He had no visual disturbances except transient diplopia on removing his glasses. He perspired profusely but had no night sweats. He had no polyuria or polydipsia; however, he complained of a sense of fullness in the epigastrium and of chronic constipation. A stereoroentgenograph of the skull which had been taken several months previously showed enlargement of the sella turcica in all diameters and slight thinning of the posterior clinoids. The patient had received 12 roentgen-ray treatments to the pituitary, the last one 2 weeks before he presented himself, but his headache had, as yet, not been alleviated.

The only significant factor in the family history was that the patient's mother was said to have died of liver disease, diabetes and hypertension. The patient was born in Siberia. In addition to the usual childhood diseases he had typhus fever at the age of 16 and a Neisserian infection at the age of 20. Also, during his 20th year a herniorrhaphy was done on the left side. One year later the resultant hypertrophied scar was excised and a tonsillectomy was done. These apparently irrelevant operations are significant in view of the nature of the patient's death during anesthesia 17 years later.

Physical examination revealed a short, stocky, muscular, swarthy and hirsute young man, (fig. 1, *D* and 1, *F*), with coarse features, large, heavy zygomatic processes, protroducing lower jaw and widely spaced teeth (fig. 1, *C*.) The height was 65.5 in. (166.5 cm.), the weight 164 lb. 74.5 kg.) and the blood pressure 110 mm. Hg systolic and 64 diastolic. In contrast to the muscular development, the lack of strength was striking. Other noteworthy findings were moderate anterior cervical lymphadenopathy, an extensive birthmark on the left thigh, and typically spade-like hands with marked hypotonicity of the fingers. Of importance also was the fact that the eyegrounds and visual fields appeared normal.

Roentgenograms of the skull showed a large, globular sella turcica, markedly hypertrophied mandible, slightly hypertrophied maxilla, enlarged antra, and prominent glabella without thickening of the cranial bones. The blood Wassermann reaction was negative; the B.M.R. was −5.9 per cent. The urine showed a specific gravity of 1.020; it contained no albumin or sugar and was normal microscopically.

Because the patient had recently received roentgen-ray therapy, treatment was confined to administration of desiccated thyroid substance, in doses of 1 grain 2 times daily, and reduction of caloric intake. In April, 1924, 4 months later, the headaches were still unrelieved but he had lost 11 lb. in weight (5 kg.) and the hands and fingers were less puffy. We then lost contact with him for 4 years. He again reported on May 21, 1928, stating that although the headaches had disappeared, prognathism and dental spacing were increasing, his eyesight had become impaired and he was troubled with backache. Upon examination the vision in the right eye was 20/20; in the left, 20/30. The fundi of both eyes revealed physiological cupping and slight temporal pallor. The visual fields were slightly flattened in the upper and outer quadrants. The B.M.R. was −9.3 per cent. Blood cholesterol was 216 mg. per cent. The glucose tolerance curve showed fasting blood sugar expressed in mg. per cent of 93; ½ hr., 126; 1 hr., 178; 2 hr., 169; the urine showed 1 + sugar in the 2-hr. specimen. Because of the suggestive blood-sugar curve, the patient was referred to the diabetic clinic for dietary control.

Despite this attempt at control, when the patient was seen one year later (May, 1929) the weight had increased to 206 lb. (93.6 kg.), a gain of 42 lb. over a 5-year period. The lower jaw protruded .5 in. anterior to the upper and showed increased spacing of the teeth. The hands and feet had become broader. He claimed that libido had increased markedly but that he had indulged in intercourse only once in 8 years because of 'fear of venereal infection.' The visual acuity had decreased (20/40 in the right eye and 20/70 in the left eye.) The fundi appeared unchanged but the visual fields, especially the left, showed definite restriction (fig. 2, *A*). Because of the beginning impairment of vision, sellar decompression was strongly considered. However, pituitary irradiation was given, instead, with the understanding that if no improvement resulted surgical intervention would be urged. After only 4 roentgen-ray treatments (approximately 625 r to each side[1]) the patient failed to return.

When the patient again reported in October, 1931, 2.5 yr. later, the weight and blood pressure were the same as before. Prognathism and spacing of teeth had increased but the size of the feet had remained unchanged. The backache which he had had for 7 years persisted. A roentgeno-

[1] For full details of roentgen-ray dosage see *Addenda*, synopsis of roentgen-ray therapy, *case 1*.

gram of the spine taken in 1926 had shown that the articular facets of the lumbar region were somewhat irregular and that the joint spaces were not clear. In a film taken at this time the appearance of both sacro-iliac joints was irregular and suggested continuous growth rather than

Fig. 1. Progression of acromegalic stigmata over 17 years; *case* 1. *A*, at 16 years of age, before onset. *B*, at 20 years, showing first evidence of slight coarsening of features. *C*, age, 23 years, when first seen. Note deepening of forehead and nasolabial folds, thickening of end of nose, spacing of teeth and broadening of wrist and fingers.

D and *F*, age 23. *E* and *G*, age 37, note broadening and deepening of chest, hirsutism, further heaviness and coarsening of features and increased prognathism. Gain of 40 lb. in weight. Characteristic cervicodorsal kyphosis is absent.

arthritic changes. The patient himself called attention to the progressive sternal bulging which necessitated the purchase of increasingly larger coats. He was still suffering from excessive perspiration and experienced drenching night sweats. Asthenia had been progressive. Lateral vision was somewhat limited, especially on the right, but he had no diplopia or photophobia. Although partial bilateral optic atrophy was noted, the visual fields had not changed appreciably since 1929 and the process in the eyes was considered as stationary. No disturbance of taste or smell could be elicited. The urine contained no sugar. The blood revealed a secondary anemia (Hb. 70%, R.B.C. 3,320,000, W.B.C. 6,600, with polymorphonuclear leucocytes 63%, lymphocytes 28%, monocytes 5%, transitionals 2% and eosinophiles 3%). The roentgenologist described the films of the skull (fig. 3) as follows:

The cranium proper is within normal limits as to size and shape. The sella turcica is deformed by an upward displacement and tilting of the anterior clinoid processes, a posterior displacement of the posterior processes and dorsum sellae, and a depression of the floor to a level below that of the sphenoidal sinus. The frontal sinus is large and the cranium anterior to it is thickened and protuberant. The mandible is enlarged throughout. The vertical portion is so long that dental occlusion is impossible and

the horizontal ramus projects forward so that the lower incisors are considerably anterior to the upper. The latter are obliquely placed apparently in an attempt to reach forward to the lower incisors. The structure of the bone of the mandible and alveolar portion of the maxilla is slightly coarser than normal. A crude estimate of the volume of space occupied by the sella turcica is about 3 to 4 times greater than normal.

Repeated assays of the urine during the preceding 2 years for the presence of anterior pituitary growth hormone were carried out in the laboratory of Dr. Herbert M. Evans[2] and had been negative. By this time it was apparent that symptomatically and objectively the endocrinopathy had progressed steadily although the headache had disappeared and visual impairment had become stationary. The patient was warned that more serious complications, notably diabetes, might develop and was urged to submit to a partial hypophysectomy. Since he refused, additional pituitary irradiation was given, a total of 2100 r in 1931 and 3600 r in 1934.

After an absence of 2.5 years, the patient reported in January, 1937, to the proctology clinic because he had a tender, painful swelling at the end of the spine which proved to be an infected pilonidal cyst. From comparison of the photographs taken in 1924 and those taken in 1937 (fig. 1, *D*, 1, *E*, 1, *F*, and 1 *G*), it was obvious that the characteristic acromegalic stigmata had progressed materially during the intervening years although no noteworthy change had occurred in the visual fields (fig. 2, *B*). Urinalysis disclosed glycosuria for the first time and the fasting blood sugar was 329 mg. per cent. Polydipsia and polyuria had been present for about 3 months. The last glucose tolerance test, performed in November, 1933, had shown the following results expressed in mg. per cent: fasting blood sugar, 102; ½ hr., 101; 1 hr., 145; and 2 hr. 168. B.M.R. was +11 per cent. Roentgenograms of the skull showed almost no change in 6 years. Roentgenograms of the hands showed increased arthritic changes at the margins of the phalangeal joints. Tufting was seen laterally, but not on the palmar or dorsal aspects. An osteochondroma had developed on the inner aspect of the upper end of the right tibia. Since an attempt to con-

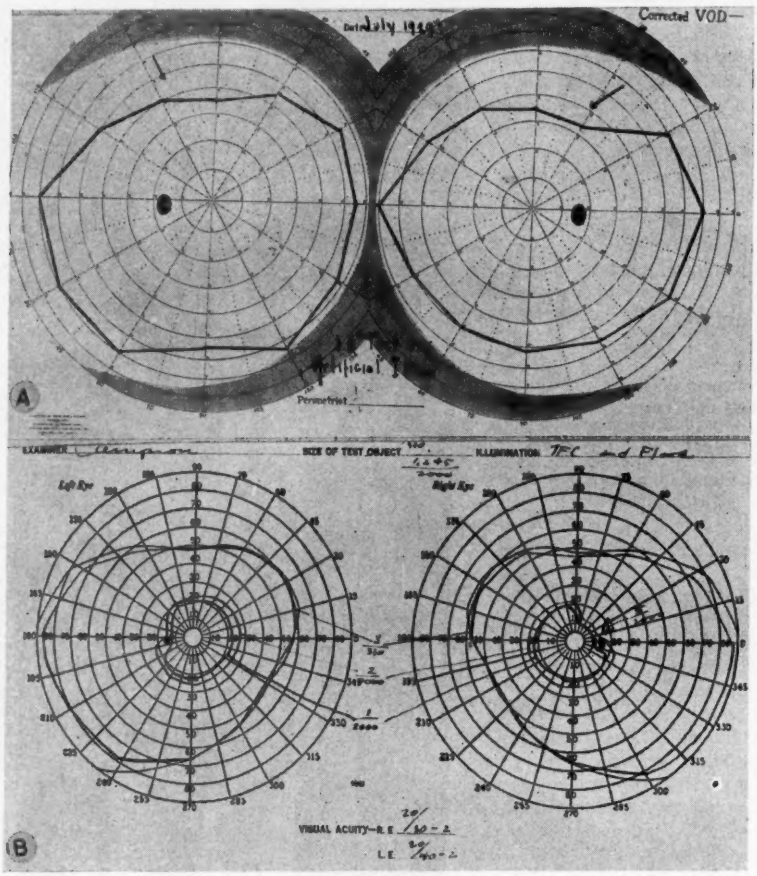

Fig. 2. PERIMETRIC CHARTS OF *case 1*. *A*, age, 29 yr. Note slight flattening of upper outer quadrants. *B*, age, 37 yr., shortly before death. Practically no change occurred in 8 years.

[2] Institute of Experimental Biology, University of California, Berkeley.

trol the diabetes while the patient was ambulatory proved unsuccessful, he was admitted to the hospital on April 13, 1939. Laboratory studies made at that time showed blood serum calcium, 10.2 mg. per cent, blood serum phosphorus, 5.38 mg. per cent; plasma cholesterol, 264.0 mg. per cent. The glucose tolerance test was interpreted as indicating a high renal threshold for glucose; the readings in mg. per cent were as follows: fasting blood sugar, 215; at ½ hr., 263; 1 hr., 330; 2 hr., 348; 3 hr., 330; 4 hr., 308; 5 hr., 230 and 6 hr., 286. All urine specimens were negative for sugar save the 2 and 3-hr. specimens which gave an olive reduction to Benedict's solution. When the patient left the hospital, for personal reasons, on April 19, the urine was sugar-free. The diet consisted of carbohydrate, 150 gm.; protein, 90 gm.; and fat, 100 gm. The insulin dose was 30-0-20 U.

The patient re-entered the hospital on April 23, 1937, and was placed on a preoperative diabetic regime. The urine and blood analyses at this time were normal. The heart measured 15 cm. to the left in the fifth interspace. The heart sounds were of fair quality. Blood pressure in mm. Hg was 110 systolic, 80 diastolic and pulse rate, 56. On April 26 the patient was taken to surgery for excision of the pilonidal cyst. Gas and oxygen anesthesia was begun at 3:20 p.m. The patient was asleep within 3 minutes. Before the incision was made he suddenly stopped breathing. Artificial respiration, adrenalin and caffein administered hypodermically and metrazol intravenously were of no avail.

Autopsy

Because this death apparently resulted from the anesthesia, the necropsy was performed by Dr. Jesse Carr of the Coroner's Office on April 26, 1937.

Gross findings. The skull showed marked occipital thickening. The brain evidenced generalized softening. The hypophysis, which was about the size of an English walnut, was smooth, gray and homogeneous with a few areas of degeneration. It lay on the optic chiasm. The left side of the sella turcica was eroded but the right side was intact. The dependent portion of the gland showed a large degenerating mass of tissue which made it impossible to remove the gland intact. The lungs were edematous and partially collapsed. The heart weighed 451 gm. (normal 350 gm.) and was normal except for moderately sclerotic vessels. It did not show the petechiae of respiratory failure. The liver was reddish-brown and congested. The spleen and pancreas were congested. The stomach was normal. The kidneys were normal except for slight congestion. Both adrenals were long, somewhat flattened and appeared enlarged. The prostate and bladder were normal. The thyroid was not palpable. The thymus was approximately 4 times normal size.

Microscopic findings. The heart muscle was edematous but otherwise normal. The lungs showed diffuse edema but no consolidation. The liver presented the appearance of cloudy swelling and some congestion. The spleen and kidneys were moderately congested. The cortical zones of the adrenals were clearly marked and showed deposits of lipoid throughout. One cortical adenoma about 2 mm. in diameter was seen. The medulla was definitely thickened and hyperplastic. The pituitary was increased in size because of the presence of an adenomatous overgrowth characterized by an extremely dense cellular background of eosinophilic cells (fig. 4, *A*). Neither fibrosis nor interacinar lymphocytes (which are so often found in thyroid glands that have been treated by roentgen-ray) were seen. The thymus appeared normal although some of Hassall's corpuscles were unusually large. Unfortunately the appearance of the thyroid, pancreas and testicles was unreported.

The pathological diagnoses were eosinophilic adenoma of the pituitary with acromegaly; acute pulmonary edema; congestion of viscera; pilonidal cyst; thymic hyperplasia; and hyperplasia of the adrenals with cortical adenomata.

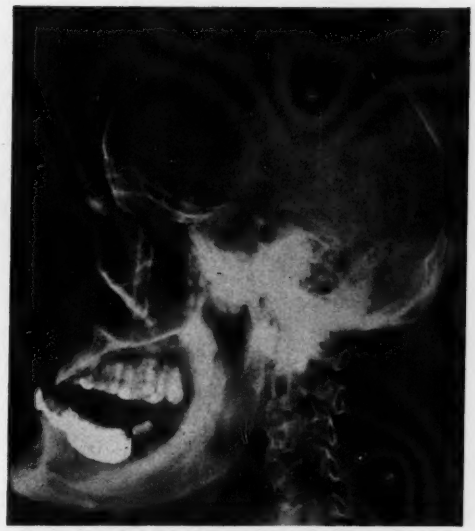

Fig. 3. Roentgenogram of skull of *case 1*. Note large sella turcica with depression of floor and displacement of clinoids; large sinuses; marked prognathism and malocclusion.

Summary

This, then, is the record of an acromegalic who died at the age of 37 years, in the 17th year of the disease. The presenting complaint was headache which failed to yield to the roentgen-ray therapy of that day (1924). The final disappearance of the cephalalgia after about a year may be attributed to spontaneous decompression of the tumor through erosion of the floor of the sella turcica. The course of the disease was characterized by steady progression of the endocrine manifestations despite roentgen-ray therapy (which had consisted of an unknown amount during 1923 and 1924 and of about 7200 r between the years 1929 and 1934). Visual impairment was slowly progressive until 1929 but was held in check thereafter.

A noteworthy observation in this case is the late onset of diabetes which appeared only 6 months prior to death. An individual with active acromegaly apparently always is a potential diabetic. The patient

died a thymic death as a result of the induction of gas and oxygen anesthesia for excision of an infected pilonidal cyst. At autopsy an enlarged thymus was found. We might speculate whether the enlargement of the thymus was the result of its failure to involute or whether regeneration and hypertrophy of thymic tissue had been stimulated by the increased production of growth hormone from the hyperplastic eosinophilic adenoma of the pituitary. The fact that prior to the onset of the disease the patient had undergone

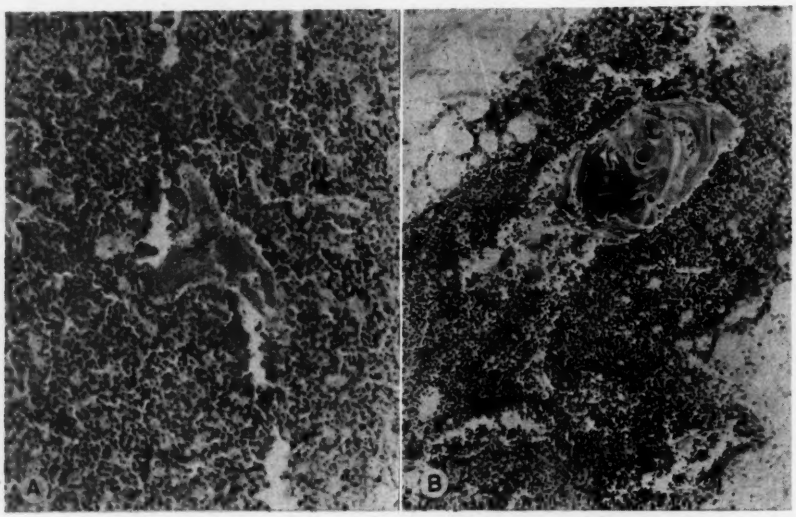

Fig. 4, A. Eosinophilic adenoma of hypophysis of *Case 1*. Note highly cellular structure and absence of fibrosis despite pituitary irradiation. ×90. *B*. Thymus. Note unusually large Hassall's corpuscle. ×90. The thymus was 3 to 4 times larger than normal for a man 37 years of age.

two surgical operations without untoward reactions would be an argument in favor of the latter hypothesis. The adrenals also were hyperplastic and showed minute cortical adenomata. The microscopic picture of the eosinophilic adenoma of the pituitary was more important for what it failed to show than what it showed. The appearance was that of an exceedingly active adenoma composed of eosinophilic cells but without the slightest evidence of fibrosis or interacinar lymphocytes which might have been expected as a result of irradiation. Thus, we are forced to the conclusion, from both clinical and pathological evidence, that the roentgen-ray therapy given in this case was woefully inadequate. One wonders whether this patient would have been spared much of the acromegalic disfigurement, the complication of diabetes mellitus and the thymic death if he had agreed to submit to subtotal hypophysectomy fairly early in the course of his disease.

Case 2 (*U. C. H. No. 87776*). Progressive, outspoken acromegaly in a man, 25 years in duration, with a remarkable degree of visceromegaly but without evidence of diabetes mellitus or of increased intracranial pressure. Exitus at the age of 45 was due to degeneration of the anterior pituitary adenoma, purulent sphenoiditis and terminal bronchopneumonia.

The patient, a 31-year-old unmarried truck driver, first entered the University of California Hospital on June 6, 1922, because of facial and skeletal changes, impairment of hearing and inability to breathe through his nose. His family history was irrelevant. His past history was not remarkable. He had sustained two broken ribs at the age of 13, which had left him with a permanent deformity of the chest, and a broken nose at the age of 16. He had had scarlet fever in childhood and typhoid fever at the age of 29.

The present illness began at the age of 19 when the patient noted a sudden and rapid increase in height and weight and found that he required increasingly larger hats and gloves (fig. 5, *B*). His hands became so large that they began to annoy and handicap him in his work. His feet did not grow as rapidly. During the intervening 11 years he had gained 111 lb. (from 145 lb. to 256 lb.). He had noted drowsiness for 3 to 4 years and difficulty in chewing due to increasing prognathism with consequent malocclusion for 2 or 3 years. Libido and potentia had not been impaired. He complained of difficulty in breathing through his nose, of dyspnea on exertion, but he had no palpitation or edema. He had an excellent appetite and a special fondness for carbohydrates. Constipation and an occasional "gas attack were his only gastrointestinal complaints. Shortly before admission he experienced increased frequency of micturition without polydipsia. Perspiration was profuse. He had had right frontal head-

aches of a sharp, shooting nature for about a year but no visual disturbances, vertigo, dizziness, convulsions or paralysis. When he held his right forearm and hand in the horizontal position, paresthesia occurred which could, however, be relieved immediately by dropping the arm.

Fig. 5. *Case 2. A, B, C,* ages 16, 20, and 26 years, respectively. *D,* age 31 when first seen in clinic. *E, F,* age 39 years. *G,* age, 45 years; after death. Note progressive deepening of forehead and nasolabial folds, progressive enlargement of nose, frontal bosses and molar eminences; increasing prognathism.

His most recent complaint, of one month's duration, was impairment of hearing.

The patient was large and obese. He had a protruding, deformed chest, slight dorsal kyphosis, a prominent abdomen and long arms. The hands were so immense that he could not obtain sufficiently large gloves (fig. 6, *A.*) The height was 74 in. (188.0 cm.) and weight was 243 lb. (110.4 kg.). The head was large and showed prominent frontal bosses and a deeply furrowed brow. The lower jaw was protuberant and massive. The hair on the head was thick and coarse while that of the eyebrows was thin and sparse especially in the lateral halves. The skin was coarse and showed considerable acne. There were seborrheic warts on the shoulders. The nose was extremely large, the skin and subcutaneous tissues were thickened and the naso-labial folds were striking. The nasal septum deviated to the right so that much of the breathing space was occluded. The pharynx was edematous and injected; the tonsils were hypertrophied and infected. The gums were boggy and retracted and the teeth showed evidence of much dental work. The tongue was large and meaty. The ears appeared normal; however, the patient could not hear the tick of a watch beyond the distance of 3 or 4 cm. on either side (normal distance about 9 cm.). The chest was normal except for the bulging of the left anterior wall. The abdomen was normal. The heart was not enlarged; the blood pressure was 120 and 65 mm. Hg. systolic and diastolic, respectively. The genitalia were normal. The extremities, however, were remarkable. The

hands were large, wide and thick with broad, stubby fingers and brittle, furrowed finger nails. The circumference of the metacarpophalangeal joints were 27.5 cm. and the length from wrist to the tip of the middle finger was 22 cm. The feet were broad and flat but were not as abnormal as the hands.

R.B.C. 4,640,000, W.B.C. 15,600 with polymorphonuclear leucocytes 72 per cent, lymphocytes 24 per cent, transitional 2 per cent eosinophiles 0 per cent and basophiles 2 per cent. The blood Wassermann reaction was negative. Roentgenograms of the skull (fig. 8) showed a thickened calvarium, a prognathic jaw, prominent oc-

Fig. 6. *Case 2.* *A* and *B*, age 31 years, when first seen. *A*, note huge paw-like hands and wide, thick feet and toes. *B*, note increased anterior-posterior diameter of chest with overgrowth of sternum and cervicodorsal kyphosis. *C*, age 45 years, at autopsy.

Neurological examination revealed the following positive findings: partial anosmia, probably due to local causes; hyperesthesia of the left eye brow to touch and pain; slight impairment of taste of the anterior two-thirds of the tongue; and slightly hyperemic fundi with somewhat enlarged veins. The discs were small and pale and the nasal margins were hazy. Visual acuity was 20/30; the visual fields showed slight encroachment in both temporal regions (fig. 7).

The laboratory data were as follows. The urine was acid, had a specific gravity of 1.030 and showed a trace of albumin but no sugar; the sediment showed a few red blood cells, white blood cells and an occasional granular cast. The blood count was as follows: Hb. 75 per cent,

cipital protuberance, and very large sinuses. The sella turcica was markedly enlarged in all diameters, suggesting the presence of an intrasellar tumor. Roentgenograms of the chest revealed scoliosis of the dorsal spine and considerable deformity of the bony thorax but no cardiomegaly.

The diagnosis of acromegaly was obvious. The neurosurgeons thought that the degree of visual impairment was not sufficient to warrant surgical intervention. Therefore the patient was discharged from the hospital with the advice to have the nasal septum straightened and to report to the Out-Patient Department for further observation.

In July, 1923, about 1 year later, the patient weighed 260 lb., a gain of 17 lb. He complained of being tired and

drowsy. B.M.R. was +9.6 per cent. Pituitary irradiation was given in two exposures to each side.[3] During 1924 he complained of increasing drowsiness. He had no polydipsia, polyuria or polyphagia. The urine contained no glucose but showed a heavy trace of albumin and numerous hyaline and granular casts. Phenolsulfophthalein test showed an output of 25 per cent at the end of the first hour, of 20 per cent at the end of the second hour and a total of 45 per cent in 2 hours. The visual fields had not changed nor had the papillitis progressed since the first examination. Roentgenogram of the skull showed the sella to be very large with irregular borders and some distortion of the anterior and posterior clinoids. The pineal gland was calcified.

From 1924 to 1929 the patient was seen frequently. No changes were observed other than an increase in the acromegalic appearance and marked narrowing of the auditory canal from bony exostoses. B.M.R. was −7.4 per cent. The glucose tolerance test gave the following readings in mg. %: fasting blood sugar, 108; ½ hr., 121; 1 hr., 118; and 2 hr., 81. In July, 1927, pituitary irradiation was again recommended but was not given. In December, 1929, assays of blood and urine for the presence of anterior pituitary growth hormone and prolan were made in the laboratory of Dr. Herbert M. Evans. The results were negative.

When the patient was seen for the last time in November, 1930, the acromegalic changes were definitely more pronounced than previously (fig. 5, *E* and 5, *F*). Since he

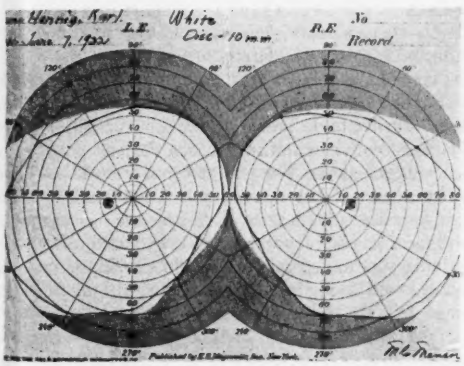

Fig. 7. *Case 2*, PERIMETRIC CHART. Note minimal narrowing of fields of vision in upper outer quadrants.

had no headache, diabetes or progression of visual impairment, no further therapy was given.

We heard nothing more of this patient until we were informed of his death in July 1936. Shortly before death intractable headache had developed. The private physician who was called on July 24 found the patient in an exceedingly restless state; however, his pulse and temperature were not remarkable. Immediate hospitalization was ordered. The patient died on arrival at St. Joseph's Hospital less than 2 hours later.

[3] For details of roentgen-ray dosage see *Addenda*, synopsis of roentgen-ray therapy, *case 2*.

Autopsy

The autopsy was performed by Dr. C. E. Smith and Dr. Dale Barbour at St. Joseph's Hospital on July 25, 1936.

Gross findings. The body was that of a middle-aged white male with advanced acromegalic changes (fig. 6 *C*).

Fig. 8. ROENTGENOGRAM OF SKULL OF *case 2*. Note prognathism, huge sinuses and large sella turcica with irregular borders and distortion of the clinoid processes.

The head was large with prominent supraorbital ridges and thick, furrowed scalp. The hair appeared to grow in rows due to this furrowing. It was short clipped, sparse in amount and coarse in texture. The nose was large and broad at the alae. The eyes were deep set. The facies were leonine. The mouth was ptotic and, together with the tongue, was drawn to the right. The lips were thick; the mouth was huge, the tongue was large with coarse papillae. The teeth showed many fillings and some spacing. The jaw was heavy and prognathous. The ears appeared to lie posterior to their normal position. The neck was short with deep transverse folds of skin anteriorly. The thorax was immense. The chest was barrel-shaped and distorted by a bony prominence at the left of the sternum. Considerable deformity of the ribs was evident. The abdomen was distended, tympanitic and showed a protruding umbilicus. The genitals appeared normal; no testicular atrophy was seen. The arms were abnormally long but not correspondingly muscular. Over the trochanteric region was seen a subcutaneous, lipomatous, dome-shaped mass which measured 7 cm. in diameter. A similar but smaller mass was inferior to it. The legs were well proportioned. The feet were very large; the palmar pads were so thick that the toes could not possibly have touched the floor.

The scalp was 9 mm. thick and lay in deep longitudinal folds. The cranial vault was thickened and the frontal sinuses were extensive. There was much subarachnoid edema over the frontal lobes and many recent friable fine adhesions were distributed over the middle fossa. The sella turcica was about 3 times normal size and appeared to be the seat of acute inflammation. The dorsum sellae was pushed backward and was so thin that it could be bent. The anterior and posterior clinoids were short. The floor of the sella was eroded in two places. The optic

chiasm was very wide. The pituitary gland was unrecognizable; it consisted of a shapeless mass of necrotic tumor or abscess. The sphenoid sinus contained much greenish-white purulent material. On the floor of the skull were many exostoses, especially over the anterior and middle fossae where plates of bone protruded into the temporal sulci. The crista Galli was very prominent. The brain weighed 1500 gm. (normal 1360 gm.) The pia arachnoid just behind the optic chiasm under the third ventricle was thickened. Sections through this region showed some petechial hemorrhages into the thalamus and small cystic cavities in the lenticular nuclei. The largest of these was not more than 2 mm. in diameter. Petechial hemorrhages, probably agonal, extended along the brain stem into the medulla. The third ventricle was somewhat dilated, although the lateral ventricles were collapsed, and the aqueduct was patent. The blood vessels appeared normal.

The thorax was well clothed. The ribs were widened, thickened and distorted. The heart was greatly enlarged; it weighed 620 gm. (normal 350 gm.). The ventricular walls were considerably hypertrophied, the left measuring 11 mm. and the right 4 mm. The right atrium contained a huge pedunculated thrombus which subtotally occluded the tricuspid orifice and was attached to the valve and chordae tendinae. The left atrium was normal. The coronary vessels were prominent and sclerotic. Atheromatous deposit was seen in the atrial surface of the mitral valve and in the aorta just above the aortic valve. The endocardium seemed to be somewhat thickened and opaque. No valvular lesions or areas of myocardial softening were seen. The pleura was smooth, moist and glistening. The left lung showed extensive bronchopneumonia throughout the lower lobe. Firm areas of consolidation were found in the right lower and the middle lobes. The mediastinal and tracheo-bronchial nodes were enlarged and anthracotic. Remnants of thymic tissue were seen in the superior mediastinum. The thyroid was enlarged, weighing 90 gm. (normal 45 gm.). It contained more colloid than normal and a few small colloid-containing areas were distinctly encapsulated. Two parathyroids were identified.

The stomach and intestines were greatly distended with gas. The peritoneum was smooth, moist and glistening. No free fluid was seen. The appendix was normal. The spleen was greatly enlarged and congested. It was septic in type. The capsule was dull and thickened in places over apparent infarcts. The pulp was soft and easily scraped away with a knife. The liver was enormous, extending over a hand's breadth below the costal margin. It weighed 6200 gm. (the largest liver previously recorded weighed 5900 gm. and normal weight is given as 1500 gm.). The cut surface showed passive congestion with nutmeg appearance. On the inferior surface of the left lobe was a sharply demarcated lighter area which extended into the substance of the liver. The gall bladder contained thin, bloody bile. Its lining appeared acutely inflamed and hemorrhagic. The pancreas showed advanced postmortem softening. The adrenals were enlarged; one contained an adenomatous area about 8 mm. in diameter. The right kidney was about two times normal size; it weighed 460 gm. (normal 300 gm.). The capsule stripped easily, leaving a surface flea-bitten in appearance. The cut surface showed marked swelling. The cortex was thickened and the pyramids were deeply congested. The pelvis showed many petechial hemorrhages. The left kidney was similar; it weighed 450 gm. The ureters and bladder were normal. The testes were soft but of normal size. The prostate was normal.

Microscopic findings. Dr. C. L. Connor made the pathological examination of the tissues after they had been fixed in formalin for a long time. Special stains could not be used, but the findings which are given were recognized without difficulty.

The heart showed large, probably hypertrophic muscle fibers. In many places the muscle had degenerated into collagenous material which had formed scars throughout the myocardium. A section of the coronary artery showed more than 50 per cent occlusion by atheromatous deposits and fibroblastic proliferation into the intima. There was no considerable infarction but the condition resembled the so-called fibrous myocarditis of arteriosclerosis.

Section of the lungs showed a marked infiltration with polymorphonuclear cells into alveoli, bronchi and bronchioles. This part of the lung was aerated in only a few rounded spaces. The condition was an example of severe acute bronchopneumonia.

In the liver patches of fat in more than moderate amount were scattered sometimes around a central vein and sometimes nearer the portal areas. Fibrous tissue was slightly but definitely increased around the lobules, in some places almost completely encircling them. There was some reduplication of the bile ducts in the portal areas with the formation of double cords of cells such as is seen in cirrhosis. No glycogen was present.

Considerable swelling and postmortem degeneration of the epithelium had taken place in the tubules of the kidneys. Some fatty infiltration was seen in the cells of the convoluted tubules. The glomeruli were large. There was slight thickening of Bowman's capsule which may have been due to the prolonged fixation. A similar collagen swelling of the interstitial tissues did not seem to be antemortem edema. The wall of blood vessels was somewhat thickened but showed only a minimal amount of proliferation of the intima. Except for the increase in size and for the lipoid deposits in the convoluted tubules, the kidneys appeared normal. No profound change from the normal was found in the testes. Mitotic figures were present in the cells of the seminiferous tubules. Cells of Leydig could be seen in small numbers in the interstitial tissue. These did not appear to be increased or decreased in number or structure.

The three parts of the pituitary gland could be identified although not all of the anterior lobe was in the section. There was no capsule around the gland and an unknown amount of tissue had been lost. What remained of the anterior lobe apparently was composed of one type of cell only which had stainable cytoplasm and was of brick-red color; these apparently were eosinophilic cells which contained granules. The fact that the cytoplasm stains at all may be considered an eosinophilic characteristic. No basophils were found. Very few cells with non-staining cytoplasm were seen (fig. 9). The thyroid contained more colloid than normal. The alveoli were generally larger but groups of smaller alveoli were present. In these, as well as in the larger ones, the cells were not flat but low cuboidal in shape. Many of the lining cells had sloughed away because of postmortem changes. Histologically, the gland

appeared to be simply hypertrophied. However, it showed more than the normal amount of connective tissue and slight infiltration with lymphocytes. The parathyroid glands contained the usual two types of cells, the chief cells being much more numerous than the eosinophils. They looked like normal glands except for their increase in size.

The *adrenals* were distorted apparently because of an overgrowth of cortical cells since the distortion was more than can be accounted for by mechanical postmortem damage. As in hyperplastic glands, the three layers of cortex were not distinct. There had been numerous localized areas of hyperplasia, some partly encapsulated and some completely encapsulated which formed so-called adenomata. At the same time some thickening of the capsule had occurred with an increase of connective tissue between cells and groups of cells in the outer cortical zone. Deeper in the cortex some islands of connective tissue with processes ramifying through the tissue were observed. These fibrotic changes no doubt represent cortical atrophy following hyperplasia and may be considered an involutionary process even though the gland was hyperplastic. It probably had been more hyperplastic at one time.

The thymus tissue was much more abundant than normal in a person 45 years of age. The mass of fat which included the thymus measured about 4 × 3 × 2 cm. A large portion of this mass was thymus tissue. It was cellular. In some parts the cortex and medulla could be distinguished. The Hassall's corpuscles were about as far apart as they would be in the thymus of a child; many were present and a few of them were calcified. The condition evidently was due either to lack of normal involution or to hyperplasia.

No important changes were observed in the brain. The cortical tissue around blood vessels was somewhat degenerated. The cysts in the basal nuclei were lined with ependyma and presumably were diverticula from the ventricles.

Pathological diagnoses were eosinophilic adenoma (degenerated) of the pituitary with marked acromegaly, marked visceromegaly, simple hypertrophy of the thyroid and parathyroid glands, and hyperplasia of the thymus and adrenals; coronary sclerosis; purulent sphenoiditis; and terminal bronchopneumonia.

Summary

In this case the unimpeded progress of acromegalic changes over a period of 26 years is recorded. The disease first manifested itself at the age of 19 with a sudden spurt of growth. When the patient died at the age of 45, he presented an advanced picture of the hideous and grotesque changes which may occur under the influence of an excessive amount of growth hormone.

Except for the urinary findings suggestive of nephritis, the condition was relatively uncomplicated. Headache and visual impairment were minimal and diabetes never developed as far as we know. We did not see the patient during the last 5 years of his life. Because, and only because, of the absence of complications, the condition was allowed to progress for 26 years. The sole therapy given was by roentgen-ray, approximately 2100 roentgens in four exposures in 1923. The sudden onset of intractable headache shortly before death may have been caused by an exacerbation of growth of the pituitary adenoma or it may have been related to the purulent infection found in the sphenoid sinus at autopsy. The immediate cause of death was terminal bronchopneumonia.

The advanced degree of visceromegaly found at autopsy is particularly noteworthy. The liver was the largest which has ever been described in acromegaly (6200 gm). The largest previously reported, by Dallemagne, weighed 5900 gm.

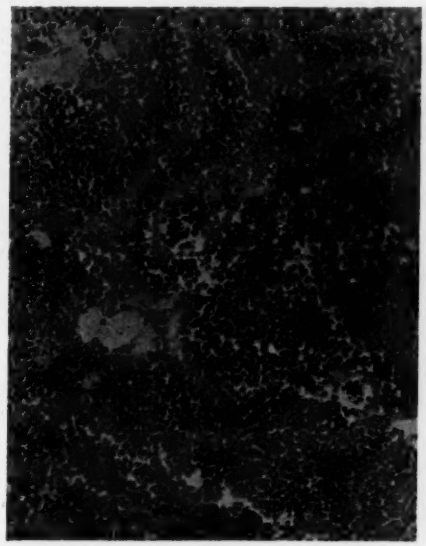

Fig. 9. Eosinophilic adenoma of hypophysis. Note closely packed cellular structure. ×95.

Case 3 (*C. H. No.* 57403). Post-menopausal onset of acromegaly in a woman, complicated by latent syphilis, arteriosclerosis, hypertension, diabetes mellitus, multiple adenomata of the thyroid, retinal detachment, breast tumor, and pseudo-tabes. Treatment consisted of pituitary irradiation in inadequate dosage. Death occurred at age 58 from degeneration and hemorrhage of the eosinophilic adenoma of the pituitary into the sphenoid sinus and the pharynx.

A widow, 56 years of age, came to the Out-Patient Department of the Hospital for Women and Children on August 22, 1934, complaining that for 4 years since her menopause, she had had increasing difficulty in locomotion associated with pain and stiffness in the knees and increasing unsteadiness of gait. She had to watch where she put her feet, could not gauge distances and was continually bumping into objects. She often staggered and frequently she fell. Vision was failing steadily, especially in the right

eye which was hemianopic. During the same interval there had been a great change in her appearance which was manifested by progressive enlargement of chin, tongue, nose, hands and feet. She neither suffered from headaches nor was she subject to respiratory infections. She had had palpitation of the heart as well as edema of the ankles for

narrow. The right pupil was smaller than the left, irregular and fixed to light although it reacted consensually. The left pupil reacted normally. The retina appeared to be detached from the temporal portion of the right eyeball. The left disc was somewhat blurred. The visual fields, determined by perimetry with a 5 mm. test object, were

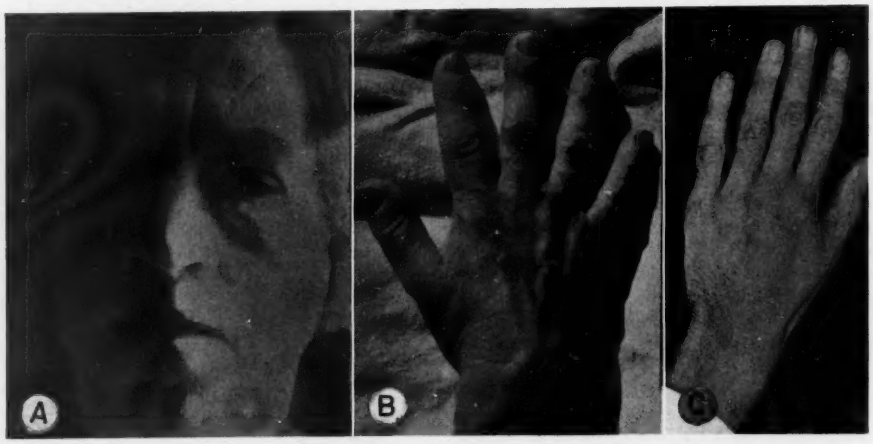

Fig. 10. *Case 3. A*, age 53 years. Note vertical furrowing and thickening of forehead, marked puffiness around eyes, narrow lid slits, thickened nose and lips. *B*, note wide wrists and fingers, thickened terminal phalanges, and thickened hypertrophied blood vessels. *C*, normal adult male hand for comparison.

4 years. She complained of much flatulence and increasing constipation. Nocturia had occurred 2 or 3 times nightly for about 4 years. She had polyuria but no polydipsia. She was always warm, perspired profusely and tired easily. She did not use any alcohol, tobacco or drugs, but drank about 5 cups of coffee and tea daily. The appetite was very good. The maximum weight of 205 lb. was attained at the onset of the illness. About 2 years before the presenting date she had been told that she had diabetes; on a special diet, to which she had adhered only for a short time, she had lost about 35 lb.

The patient was married at the age of 15. Her husband met an accidental death 14 years later. Of 8 pregnancies, 2 terminated in spontaneous abortions. Three children died in infancy. The three living children were 40, 34 and 29 years of age, respectively. The daughter aged 40 had syphilis which may have been congenital. At the age of 54 years the patient had had a moderately severe attack of broncho-pneumonia. Menstruation had begun at the age of 13, periods had occurred every 28 days, had lasted for 5 to 6 days and had been characterized by profuse flow. The menopause was complete at 52 years of age.

The patient presented a typically acromegalic appearance. She had large coarse features, deeply furrowed brow, protruding mandible, prominent frontal bosses, hypertrophic nose and large, spade-like hands (fig. 10, *A* and 10, *B*). The height was 62.5 in. and the weight 170 lb. The skin was thick, dry and coarse. She had several pedunculated fibromata on the neck, a large one on the inner aspect of the right thigh and one on the dorsum of the left foot. The eyelids were puffy and the eye slits

normal save for a large nasal defect on the right which may have been due to the retinal detachment. Except for hypertrophy, the nose was normal. The lips were thick and the lower jaw was prognathic. The teeth in the lower jaw were spaced widely and in poor condition; marked periodontitis was present. The upper jaw was edentulous. The tongue was very large and was traversed by a deep midline fissure. The nasopharynx was slightly injected. The tonsils were small and cryptic. The submaxillary, axillary, inguinal and epitrochlear lymph nodes were enlarged. The thyroid was nodular and considerably enlarged. The thorax was barrel-shaped; the sternum was thickened and protruding. The breasts were soft and full but showed no masses or tenderness; the nipples were inverted. The lungs were normal by percussion and auscultation. The heart was considerably enlarged; the point of maximum impulse was in the 6th interspace at the anterior axillary line. A systolic murmur was heard over the entire precordium; it was loudest over the aortic and mitral areas. The systolic blood pressure was 180, the diastolic, 100 mm. Hg. The rounded edge of the liver was palpated about 4 cm. below the costal margin. The hands were large and spade-like. The thickening involved especially the terminal phalanges. The feet were broad and thick. The ankles showed slight pitting edema. The veins and arteries of the upper and lower extremities were hypertrophied and tortuous. Considerable cervicodorsal kyphosis and moderate lumbar lordosis with accompanying limitation of motion were observed. The vaginal outlet was relaxed. A pea-sized fibroma, similar to the fibromata of the skin, was found just inside the introitus.

A considerable amount of yellow discharge was noted. Advanced senile vaginitis was evidenced by adhesions of the vault which obliterated the fornices. The uterus was small, anteriorly situated and freely movable. The adnexae were normal.

The patient's gait was markedly ataxic; she put down her feet in an unsteady manner. The Romberg sign was positive; the patient staggered in all directions. The muscles showed no weakness, atrophy or fibrillation. All movements were performed sluggishly. Taste and smell were normal. There was slight impairment of sensation in the right extremities. The tendon reflexes were equal and active. Clonus and the Babinski sign were absent. Position sense was intact. The ataxia was confined to the lower extremities; the finger-to-nose test was well done whereas the heel-to-knee test was poorly done.

The significant observations made by laboratory examination were as follows. The urine, examined on Aug. 28, 1934, showed a faint trace of albumin, no sugar, many calcium oxalate crystals, numerous white blood cells and 4 to 5 red blood cells per high dry field. Two weeks later 3+ sugar was found in the urine. The blood count showed: Hb. 97 per cent (Sahli), R.B.C. 5,300,000, W.B.C. 6000, with polymorphonuclear leucocytes 60 per cent, lymphocytes 39 per cent and transitional 1 per cent. Fasting blood sugar was 296.2 mg. per cent. The blood Wassermann reaction was 3+ in three dilutions (Kolmer). B.M.R. was +22 per cent. By electrocardiographic examination of the heart, the rate was 72, the rhythm was regular and of normal sinus origin. The PR interval was 0.16 and the QRS was 0.08 seconds. The P-waves were moderately broad and notched and there was evidence of left preponderance consistent with a hypertensive heart.

Stereoroentgenographs of the skull showed that the calvarium was thick and the bony texture was coarse and dense. The sella turcica was enlarged but the floor and the clinoids were intact. The pineal body was densely calcified but not noticeably displaced. The frontal sinuses were strikingly enlarged (fig. 11). Roentgenograms of the hands showed thickening of the bones with characteristic tufting of all terminal phalanges. The knee joints showed rather extensive hypertrophic changes, but no evidence of a destructive lesion. Fluoroscopic examination of the chest revealed a rounded shadow above the arch of the aorta which suggested a substernal extension of the thyroid. The arch of the aorta was sclerotic and wide in the antero-posterior view, partly due to rotation. The heart appeared hypertrophied especially in the anterior-posterior diameter.

On the basis of the physical findings the following diagnoses were made: pituitary tumor with acromegaly; diabetes mellitus; latent syphilis; arteriosclerosis with hypertension and cardiac hypertrophy; multiple adenomata of the thyroid; retinal detachment of the right eye; multiple fibromata; varicosities; senile vaginitis; and chronic hypertrophic arthritis. Most of the complications of acromegaly as well as a few extraneous conditions were evident in this case.

Treatment of this patient was difficult because of her failure to cooperate. It consisted of dietary management of the diabetes and control of the syphilis by administration of bismuth salicylate intramuscularly and potassium iodide orally. Since the patient did not adhere to the diet, the urine never was consistently free of sugar. In February, 1935, following a severe acute upper respiratory infection, the patient was hospitalized for control of diabetes. A glucose tolerance test gave the following results in mg. per cent: fasting blood sugar, 234; at ½ hr., 284; 1 hr., 332; 2 hr., 346; and 3 hr. 206. The quantitative urinary sugar was 8.6 gm. or 3.8 per cent. The blood cholesterol was 146.4 mg per cent; the B.M.R. was +36 per cent. Lumbar puncture yielded a clear, colorless fluid under a pressure of 210 mm. of water, sugar of 110 mg. per cent, a cell count of 10 with 50 per cent polymorphonuclears and 50 per cent lymphocytes, negative Wassermann and Pandy reactions, a slightly positive Nonne and a gold curve of 0111211000.

Fig. 11. ROENTGENOGRAM OF SKULL OF *case* 3. Note thickened calvarium, huge frontal sinuses, prognathism and enlarged sella turcica.

After a week's hospitalization the patient was discharged with sugar-free urine, on a diet which consisted of carbohydrate, 100 gm.; protein, 65 gm.; and fat, 100 gm. (a total of 1566 calories), without insulin. Three months later the urine still was sugar-free; the fasting blood sugar was 190.4 mg per cent. Since the diabetes and syphilis were under control, pituitary irradiation was begun. After 3 roentgen-ray treatments to the region of the hypophysis, the patient volunteered the information that her shoes seemed large and that her hands were less puffy than previously. The adenoma of the thyroid was definitely smaller, but this may have been an iodide effect. Roentgen-ray therapy was continued until a total of 800 r had been given to each side. The last treatment was given on August 20, 1935.[4]

Four months later, in December, 1935, the patient had a severe upper respiratory infection which persisted for 11 days. Following this illness a very hard, painless mass about the size of an egg appeared just below the nipple of the right breast. It was attached to the overlying reddened skin. A large lymph node was palpable in the right axilla. The left nipple was inverted and a small firm lump was observed beneath and medial to it. Both nodules were opaque to transillumination. The condition suggested carcinoma. Surgical exploration was to be done

[4] For details of roentgen-ray dosage see *Addenda*, synopsis of roentgen-ray therapy, *case* 3.

after a few days of treatment with hot compresses to allow the inflammatory reaction to subside. The patient failed to return until 9 days later at which time the mass was smaller and more rubbery. One month later the mass had disappeared and the diagnosis was revised to inflammatory mastitis.

Early in 1936 the patient again was hospitalized for control of diabetes. The fasting blood sugar was 285.6 mg. per cent and the cholesterol 303 mg. per cent. When she was dismissed on Feb. 29, 1936, the urine sugar-free, on a diet consisting of carbohydrate, 110 gm.; protein, 70 gm.; and fat, 100 gm. (a total of 1620 calories) and insulin 12-0-12 U, the fasting blood sugar had dropped to 153.8 mg. per cent and the blood cholesterol to 250.5 mg. per cent. From this time on the patient became completely discouraged and unco-operative. Whether the necessity for injections of insulin was responsible for her attitude is difficult to say. Her condition became steadily worse. Finally, on Sept. 30, 1936, she entered the San Francisco Hospital in coma with temperature of 104.6°F. For several weeks before entry she had vomited and had suffered from severe headache. She was said to have lost the lateral field of vision in the left eye. On examination the left pupil was dilated and failed to react to light. A choked disc was observed in the left fundus. She had bleeding from the left side of the pharynx. The blood pressure was 240 and 100 mm. Hg systolic and diastolic, respectively. The knee jerk reflexes were diminished. A blood count showed: Hb. 98 per cent, R.B.C. 6,000,000, W.B.C. 12,200 and a normal differential count. The spinal fluid contained 27,000 cells of which 45 per cent were red blood cells and the remainder were polymorphonuclear cells. The patient died on Oct. 1, 1936, without having regained consciousness.

Autopsy

Gross findings. The body was that of an obese, grey haired, acromegalic female about 50 years of age. Distribution of the hair was normal. The right pupil measured about 3 mm. and the left about 5 mm. in diameter. The nasal septum was intact. The upper jaw was edentulous; several teeth were missing from the lower jaw; those remaining were fairly well preserved. The tongue was large. There was a blood clot in the pharynx on the left side but no bleeding point was seen. A movable mass about 3 cm. in diameter which was not attached to the skin was seen under the ramus of the jaw on the right. The trachea was in the midline. The breasts were small and showed inverted nipples. The chest and abdomen were not remarkable. The genitalia appeared normal. The lower extremities were relatively normal but the upper ones were disproportionately long, extending to the middle of the thigh. The hands were exceedingly large with huge phalangeal joints and clubbed fingers. There were several papillary skin lesions over the body, some extending as far out as 2 cm.

The scalp stripped from the skull with ease. The calvarium was thickened, measuring 1 cm. at one point but the bone was rather soft and could be sawed with ease. The meninges were normal. The brain weighed 1250 gm. (normal 1360 gm.). Its surface appeared normal. No palpable tumors were found within the brain substance. The anterior and posterior clinoid processes were eroded away. The sella turcica was deepened and filled with the enlarged pituitary gland which had penetrated through the floor into the sphenoid sinus and at one point into the pharynx. At this point bleeding was observed. The pituitary was approximately 4 times normal size and weighed 12 gm. It was soft, congested and had no distinct form. The thyroid was enlarged and congested. The left lobe weighed 45 gm. and the right 55 gm. (normal total weight 45 gm.).

The pleural cavity contained no free fluid but adhesions were seen between the apex of the left lung and the rib cage. The left lung was subcrepitant throughout. The bronchi appeared normal. The pulmonary vein contained no antemortem clot. The lymph nodes were small and anthracotic. On cut section the lung was somewhat congested and the apex was slightly scarred. No areas of consolidation were seen. The right lung was similar to the left.

The pericardial cavity was obliterated by dense, firm adhesions. The heart with adherent pericardium weighed 525 gm. (normal 250 gm.). The right ventricle measured 4 mm. and the left 5 mm. in thickness. The endocardium was smooth throughout. The valves were normal. The auricles contained no antemortem clots. The coronary arteries showed considerable arteriosclerosis but no obliteration or narrowing.

The abdominal cavity contained no free fluid. The serosal surfaces were smooth and shiny. The appendix was bound to the parietal wall by dense, firm adhesions. One adhesion was observed between the gall bladder and the large bowel. The diaphragm extended to the 5th interspace on the right and to the 5th rib on the left. The liver did not extend below the costal margin. It measured 30 × 25 × 8 cm. and weighed 2350 gm. (normal 1500 gm.). Its surface was smooth except for a plaque of scar tissue 3 × 4 cm. in the left lobe. The parenchyma under the scar tissue was dense and firm and cut with resistance while that of the liver in general was rather pale and showed fatty trabeculations. The gall bladder contained 30 cc. of tan-colored bile. The biliary passages were patent. The spleen weighed 460 gm. (normal 200 gm.) and measured 18 × 9 × 3 cm. Its surface was smooth and on cut section appeared congested. The left kidney was pale, weighed 245 gm. (normal 300 gm.) and stripped with great difficulty. The cortex was 8 mm. thick. It contained a normal amount of perirenal fat. The renal pelvis was normal. The right kidney weighed 240 gm. and resembled the left. The adrenals appeared normal in size and shape. The left weighed 5 gm. and the right 15 gm. The pancreas was normal. The aorta was sclerotic throughout its entire length. The spinal cord in the lumbar region appeared normal. The small and large bowels contained dark, bloody material. The vaginal wall was thickened throughout, with small plaques of dense fibrous tissue. The cervix was atrophic and the os was patent. The uterus was normal in thickness but contained two papillomata in the mucosa. The fallopian tubes were apparently normal. The ovaries were approximately normal in size but were firm and almost stony in consistency.

Microscopic findings. In the brain numerous calcarious bodies were observed in the choroid plexus of the left posterior horn of the ventricle. The meninges at the base

of the brain were congested and contained moderate numbers of polymorphonuclear leucocytes. The hypothalamus contained numerous amylaceous bodies. The tissue was loose and there were a few round cells about several of the vessels. The pituitary (fig. 12) was replaced largely by hemorrhagic necrotic debris and great numbers of polymorphonuclear leucocytes. The acini which remained intact stained pink with hematoxylin and eosin and were widely separated by edema and hemorrhage as well as infiltrated by red blood cells and polymorphonuclear leucocytes. The overlying meninges were thickened with fibrous tissue and also were heavily infiltrated with the same type of cells. The submaxillary mass showed increased fibrous tissue reaction about lymphoid elements. The polypoid mass in the skin was covered by normal epithelium and was composed of masses of hyalinized fibrous tissue. The acini of the thyroid were lined with cuboidal epithelium and filled with pink-staining colloid. An increased amount of interlobar connective tissue was noted indicating involution, perhaps of a previous hyperplasia.

The fibrous tissue strands between the muscle fibers of the heart were moderately increased. The pericardium showed fibrous tissue thickening. There was a generous sprinkling of round cells and polymorphonuclear leucocytes among the muscle bundles. A large calcarious plaque was seen in the intima of the aorta. Slight scarring about the vasa vasorum and a few round cells were present. The aveolar walls of the lungs were congested and the alveoli contained debris and occasional red blood cells and leucocytes. The septae contained fibrous tissue.

The liver showed marked increase in perilobar connective tissue of the cells and contained increased fat. The wall of the gall blader was edematous and showed fibrous tissue thickening. Small collections of round cells were present in the mucosa the villi of which were thickened and adherent to one another. A large artery in the wall contained collections of round cells about the vasa vasorum. The pulp of the spleen was congested and infiltrated with polymorphonuclear leucocytes. The vessels of the pancreas were congested; only a few small islets were present. The kidneys contained small collections of round cells under the capsule and about some of the congested blood vessels. The glomeruli were large but otherwise normal. An occasional hyaline cast was seen in the tubules. The adrenals were normal.

The breasts showed ducts which appeared to be dilated. One duct was filled with an intracanalicular mass of fibrous tissue and had no lining epithelium. Large foci of round cells were seen about the ducts and acini. No follicles of germinal epithelium were present in the ovaries. The ovarian tissue was replaced by corpora albicantes and fibrous tissue. The uterus showed atrophic endometrial glands some of which had become cystic and were lined by low columnar epithelium and were filled with pink-staining debris. The uterine muscle was fibrotic. The salpinx showed a slight increase in the connective tissue of the fimbriae. Underlying the atrophic epithelium of the vagina were numerous round cells. The spinal cord was riddled with small amylaceous bodies. The cells of the dorsal column and anterior horn were normal. The meningeal vessels were congested but showed no inflammatory change.

The pathological diagnoses were eosinophilic adenoma of the pituitary with perforation of the sphenoid sinus and hemorrhage into the pharynx; acromegaly; acute basilar meningitis; simple nodular goiter; chronic adhesive pericarditis; generalized arteriosclerosis with cardiac hypertrophy; multiple polypi of the uterus; multiple fibromata of the skin; chronic cystic mastitis; intracanalicular fibroma of the breast; chronic cholecystitis; healed apical pulmonary tuberculosis; and chronic submaxillary lymphadenitis.

Summary

The onset of acromegaly in this case occurred at the age of 52 years, following the menopause. The duration of the disease was 6 years. Death was due to hemorrhagic necrosis of the pituitary adenoma with extension through the sellar floor into the sphenoid sinus, and hemorrhage into the pharynx. The symptoms were acral enlargement, difficulties with locomotion, failing vision, polyphagia, polyuria and profuse perspiration. Headache appeared terminally.

The complications were numerous and confusing. Diabetes appeared early in the course of the disease, having been diagnosed 2 years after the onset. It was poorly controlled. The visual field defect, which is so characteristic of pituitary tumors, was due in this case to a retinal detachment. This complication has been reported only once before in acromegaly in a recent article by Flaum and Ralli (9). The presenting complaint of locomotive difficulties of an ataxic nature and the positive serology were suggestive of tabes. Closer study showed that it was undoubtedly a pseudo-tabes which has been described previously in conjunction with acromegaly. The cardiac symptoms and findings were difficult to evaluate during life. How much of the symptomatology was due to arteriosclerosis and hypertension, how much to the visceromegaly which is an integral part of acromegaly, how

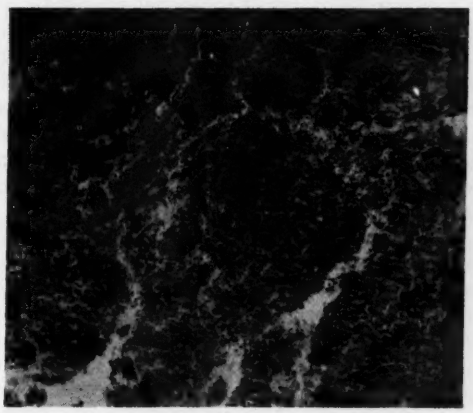

Fig. 12. *Case* 3. EOSINOPHILIC ADENOMA OF THE HYPOPHYSIS. Note degeneration and areas of hemorrhage and edema. ×120.

much to the mildly toxic adenomata of the thyroid, and how much to syphilis, was difficult to establish. The syphilis probably was latent and of long standing. Atkinson (6) in his searching compilation reported the incidence of syphilis in acromegaly as about 10 per cent. Since the same incidence occurs in the general population, we may conclude that the association of syphilis with acromegaly in this case was purely coincidental. Another complication was the mass in the left breast which made its appearance not long after pituitary irradiation was begun. It was at first considered to be carcinomatous but eventually proved to be an intracanalicular fibroma associated with chronic cystic mastitis. Therapy was difficult to carry out because of the poor cooperation of the patient. It consisted of dietary control with and without insulin for the diabetes, bismuth salicylate administered intramuscularly and potassium iodide orally for the syphilis, and an inadequate amount of irradiation (consisting of 1600 roentgens) to the hypophysis which caused prompt although transient improvement.

Case 4 (U. C. H. No. 15477). Acromegaly of about 19 years' duration in a woman, with early and persistent amenorrhea, blindness and diabetes mellitus, treated by transphenoidal partial hypophysectomy and inadequate pituitary irradiation which resulted in partial restoration of vision but had no effect on amenorrhea or diabetes. Xanthoma diabeticorum was a complication. Death occurred at age 43 by suicide.

The patient, a single woman 33 years of age, was born in Minnesota of American parents of French-Norwegian extraction. She first came to the Out-Patient Department of the University of California Hospital on Oct. 5, 1928, complaining of general weakness of 3 to 4 months' duration. The family history was non-contributory. The past history was negative except that she had had small-pox at the age of 10, pertussis as a young child and again at the age of 15, and measles at the age of 20. Catamemia, which had begun at the age of 13, had been normal. Regular periods occurred at 28-day intervals and lasted 4 days. The amount of flow was normal.

A resumé of the symptoms pertaining to the patient's complaint revealed the following sequence of events. Menstrual irregularity began at 24 years of age and progressed to complete amenorrhea at the age of 25. Simultaneously right-sided facial 'neuralgia' occurred at about monthly intervals. Size of hands and feet increased at the age of 30; the patient's attention was first attracted to it because of increasing difficulty in playing the violin, but she attributed the trouble to heavy work. Vision began to fail, at first in the right eye and later in the left eye (an optician had trouble in finding a spectacle frame wide enough to bridge her face). In spite of these difficulties the patient considered herself well until 3 to 4 months prior to the presenting date at which time she was forced to stop work as a power machine operator because of extreme nervousness, irritability and weakness. Sleep was disturbed by severe noctidrosis. The appetite, which had always been good, had become excessive and she had gained 37 lb. in 4 years (112 to 149 lb.) She admitted a slight increase in thirst but she had not had polyuria. She had suffered from constipation, chronic nasal catarrh and tinitus aurium for many years. For 2 to 3 months she had experienced some headache.

The patient's height was 64 in. (162.2 cm.) and the weight 149.5 lb. (68 kg.). She was typically acromegalic in appearance (fig. 13, *E*) with marked prognathism of the lower jaw, prominent malar eminences, wide nose and full lips. The brow was low and broad with heavy, wrinkled folds and prominent frontal bosses. Tenderness was elicited over the right mastoid and the right frontal region. The complexion was swarthy with numerous dark, pigmented spots. The hair was kinky. Despite the patient's purported French-Norwegian ancestry, she was definitely negroid in appearance (fig. 13, *B*). The eyes were widely separated, the upper lids were puffy and there was a tendency to a nasal brow. Slight exophthalmos was present, the right eye being somewhat more prominent than the left. Intraocular tension was increased. The right pupil was circular, regular and responded sluggishly to light and accommodation. The left pupil also was round and regular in outline but was widely dilated and responded only consensually to light. There was lateral nystagmus both to the right and to the left. The extrinsic muscles responded normally although a suggestive von Graefe sign was present on the left and convergence was poor. Visual acuity on the right was 20/70–2 while with the left eye the patient could barely detect light. The right fundus was normal but the left showed a completely atrophic disc. The fields were limited to nasal vision in the right eye (fig. 14, *A*). The teeth were widely spaced, the jaws did not approximate properly and oral hygiene was poor. The tongue was huge, being both wide and long. The tonsils were hypertrophied, the right more so than the left. Large submaxillary lymph nodes were palpable bilaterally. The thyroid was smooth, symmetrical and moderately enlarged, without nodules, thrill or bruit. The costal margin was flared. The breasts were moderately well developed. The lungs were normal and the heart was normal save for its slow rate (58 per minute). The blood pressure was 122 and 90 mm. Hg, systolic and diastolic, respectively. The abdomen was normal except for mild tenderness over McBurney's point. The hands were broad with long, flat, wide fingers. The joints were astonishingly supple. The feet were broad. The toes were exceedingly wide. The tendon reflexes were normal. Slight cervicodorsal kyphosis was present. The external genitalia were normal. The hymen was intact. On rectal examination the cervix was palpated posteriorly. The uterus was not palpated clearly but showed no tenderness or abnormal masses.

The urine had a specific gravity of 1.025, no albumin 1 + sugar and negative microscopic findings. The glucose tolerance test gave the following results in mg. per cent: fasting blood sugar, 116; ½ hr., 206; 1 hr., 217; 2 hr., 206; the urine showed 1 + sugar in the fasting, ½-hr. and 1-hr. specimens and 2 + sugar in the 2-hr. specimen. B.M.R. was −4.1 per cent. The blood Wassermann reaction was negative. Roentgenogram of the skull showed marked enlargement of the sella turcica with thinning of the anterior and posterior clinoid processes and depression

Fig. 13, *A*, *B*, *C*. *Case 4*. *A*, age, 24 years; just prior to onset of acromegaly. *B*, age, 33 years, when first seen. *C*, age, 38 years. Note startling change in features, especially the nose, lips and forehead, also the pigmentation and darker frizzier hair.

of the floor. The lower jaw was typically acromegalic (fig. 15, *A*). Roentgenogram of the hands (fig. 15, *B*) and feet showed tufting of the distal phalanges and exostoses of both great toes. Bony defects were seen in the terminal phalanges of both thumbs at corresponding points and in the left fifth digit at the proximal interphalangeal joint. Roentgenogram of the chest did not reveal cardiomegaly.

The diagnoses, made on basis of the physical and laboratory investigations, were: pituitary tumor impinging on the optic chiasm and causing blindness on the left and temporal hemianopsia on the right; acromegaly; and diabetes.

On Oct. 24, 1928, a transphenoidal decompression was performed by Dr. Howard Fleming. After the sphenoidal sinus had been exposed and the anterior wall removed, a glandular type of tissue extruded. A piece about the size of a marble was removed in bits. On microscopic section this tissue showed sheets of cells without pattern in a capillary stroma. The cells had round vesicular nuclei and faintly staining grey to pinkish-grey cytoplasm without definite membranes. No basophils and only a few acidophils were present. Although the predominant cells had a non-staining cytoplasm, Dr. C. L. Connor, the pathologist, concluded that the tumor probably was an acidophilic adenoma, struma or hyperplasia. Recovery from the operation was uneventful. The patient was discharged from the hospital on Nov. 10, 1928, after having received 4 roentgen-ray treatments to the pituitary region, or about 700 r to each side.[5] At this time the B.M.R. was −1.5 per cent and the glucose tolerance test gave the following readings in mg. per cent: fasting blood sugar, 93; ½ hr., 207; 1 hr., 256; and 2 hr., 210.

Three months later the patient's vision was much improved (fig. 14, *B*), the night sweats and headache had disappeared, the hands seemed smaller and the face less thick, suggesting a decrease in the so-called acromegalic myxedema. However, menstruation had not returned nor had any improvement in diabetes taken place. As a matter of fact, sugar tolerance was depressed further by the complication of a pulmonary abscess which required 5 weeks' hospitalization (May 14, 1929 to June 16, 1929). The patient was discharged cured of the abscess and the urine sugar-free, on a diet of carbohydrate, 90 gm.; protein, 90

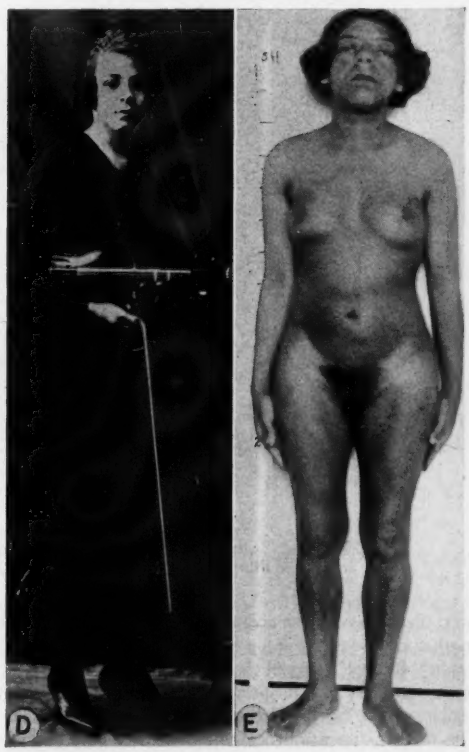

Fig. 13, *D*, *E*. *Case 4*. *D*, patient at age of 24, just prior to onset of acromegaly. *E*, age, 33 years, when first seen.

[5] For details of roentgen-ray dosage see *Addenda*, synopsis of roentgen-ray therapy, *case 4*.

gm.; and fat, 120 gm. (a total of 1800 calories), without insulin. Nevertheless, 3 months later (Sept. 20, 1929) the fasting blood sugar was 333 mg. per cent with an orange reduction of the urine to Benedict's solution. Finally, she was stabilized on a diet consisting of carbohydrate, 90 gm.; protein, 90 gm.; and fat, 100 gm., with insulin 25-10-15 U. Because of the increasing severity of the diabetes another course of pituitary irradiation was given (about 1750 r). By Dec. 4, 1929, the insulin requirement had increased to 35-25-30 U in spite of the weighed diet. On December 10, the fasting blood sugar was 472 mg. per cent. The patient discontinued taking insulin on Jan. 1, 1930, and failed to return until she was brought to the hospital in diabetic acidosis on March 21. Two weeks later she was discharged, urine sugar-free, on a diet consisting of carbohydrate, 100 gm.; protein, 60 gm.; and fat, 120 gm., with insulin 25-5-20 U. The B.M.R. at this time was −21.9 per cent.

From 1930 to 1935 the patient got along fairly well. The smooth course was marred only by the occurrence in 1932 of a diffuse disseminated xanthomatosis which lasted for about 6 months. The full details of this complication were reported in 1933 by McGavack and Shepardson (10). The maximum improvement of vision was reached in February, 1934, when the visual acuity was 20/30 in the right and 20/70 in the left (fig. 14 C). In 1931, samples of blood were sent to the laboratory of Dr. Herbert M. Evans for assay of growth hormone; none was found. In 1933 the

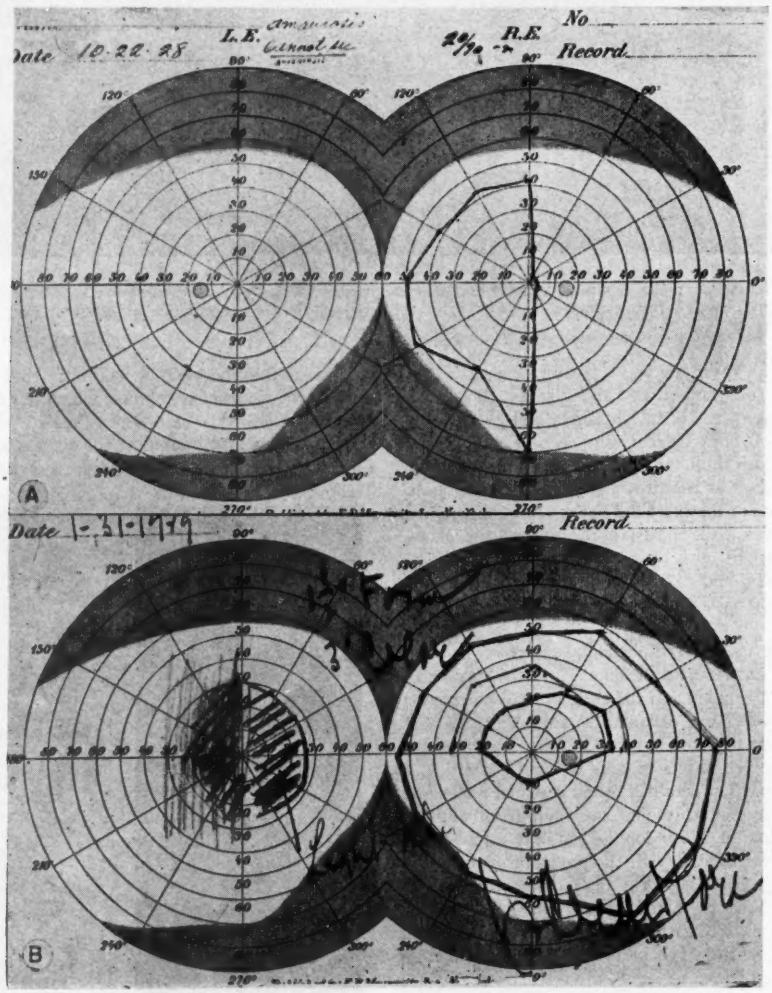

Fig. 14, A. Perimetric chart of *case 4* at age of 33. Note amaurosis of left eye and hemianopsia of right eye. B, field of vision 3 months after transphenoidal partial hypophysectomy and minimal amount of pituitary irradiation. Note improvement.

patient was for the first time described as a negress.

Between 1935 and 1938, although the diabetes was well controlled, the acromegalic signs increased and a slow but progressive diminution in visual acuity of the right eye became apparent. Roentgenograms of the skull showed further enlargement of the sella turcica and tilting of the posterior clinoids. On Jan. 11, 1938, the patient was seen in consultation with Dr. Howard Naffziger who advised surgical treatment. This the patient refused because of her mother's illness. By March, 1938, she was suffering from persistent headache and intractable vomiting. Visual acuity had diminished to 20/200 in the right eye while in the left eye she could discern light only (fig. 14, *D*). Between 21 and May 4, she received almost daily roentgen-ray treatments to the hypophyseal region, 850 r to the left side and anterior field and 900 r to the right lateral field, or a total of 2600 r. The effectiveness of these treatments is not known since on May 21, 1938, at the age of 43, the patient ended her life by taking poison.

Autopsy

Gross findings. The autopsy was performed by Dr. Jesse Carr, of the Coroner's office. The body was described as that of a negress with black, kinky hair and an old scar on the left side of the chest posteriorly. The lungs showed a few old apical adhesions. The heart presented a few tiny sub-epicardial petechiae. The coronary arteries were extremely sclerotic throughout and in some areas showed 75 per cent occlusion. The cardiac valves and aorta were slightly sclerotic. There was an area of fibrosis, 1 × .5 in. wide, in the posterior wall of the left ventricle. The liver showed moderate passive congestion and fatty replacement. The gall bladder, spleen and pancreas were normal. The kidneys were large, pale and greasy. The

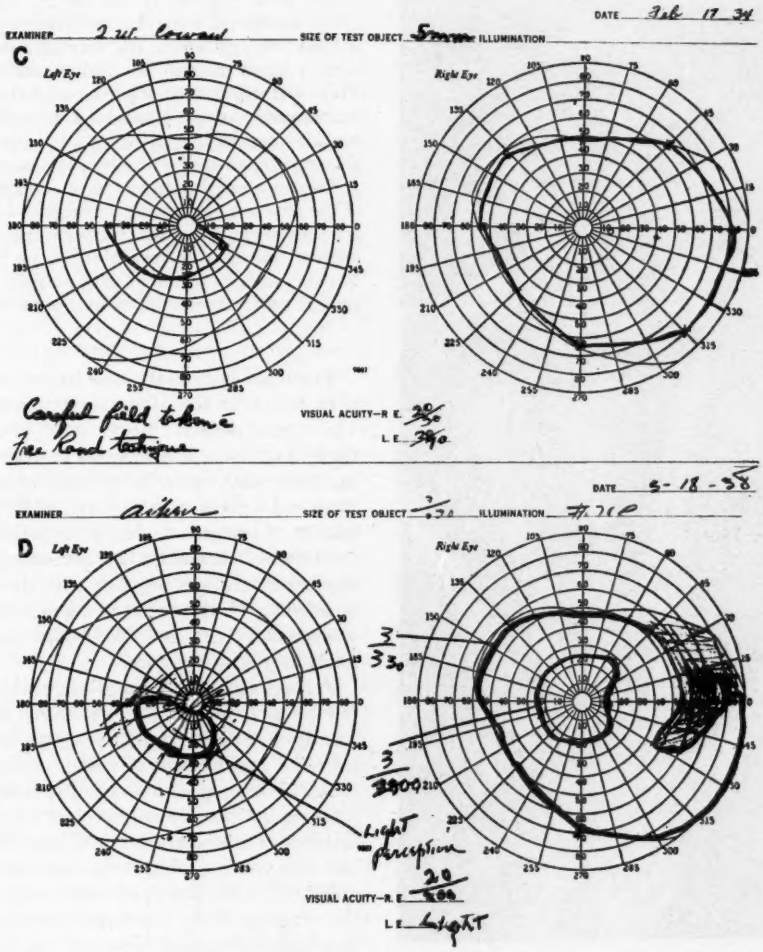

Fig 14. C. PERIMETRIC CHART OF *case 4* at age of 39. Note maximum improvement in visual fields and acuity. *D*, visual fields 2 months prior to death.

Fig. 15. A. Roentgenogram of skull of *case 4*. Note large sinuses, prognathism and large bulging sella with depressed floor and thinning of anterior and posterior clinoid processes. B. Roentgenogram of hand of *case 4*. Note characteristic tufting of terminal phalanges and osseous defects in distal phalanx of thumb.

stomach showed many tiny petechial hemorrhages. The appendix was normal. About 3 ft. above the cecum a Meckel's diverticulum 4 in. in length was seen. The intestines contained a yellowish liquid and a few tiny petechial hemorrhages. The uterus was atrophic and the ovaries were small and sclerotic. The scalp and skull were normal. The brain weighed 1500 gm. and measured 16 × 15 × 10 cm. There was moderate sclerosis at the base and some edema throughout. The pituitary measured 4 cm. in diameter and was the site of a tremendous overgrowth which had caused great pressure upon the optic chiasm.

Microscopic findings. The pituitary gland was edematous. It consisted of heavy masses of small round cells with small nuclei and pink eosinophilic granules. A slight amount of fibrosis was evident (fig. 16). The breasts contained dense hyaline stroma which supported small glands and dilated ducts that were surrounded by diffuse lymphocytic infiltration. The adrenals showed abundant cortical lipoid material but had normal cortical zones. There was some brown degeneration in the medulla. The ovaries presented the picture of a dense stroma without evidence of germinal epithelium or follicular development. Two small cysts lined with epithelium were seen.

The pathological diagnoses were eosinophilic adenoma of the pituitary gland with acromegaly; advanced coronary sclerosis with subtotal occlusion and myocardial infarction; bilateral apical pleural adhesions; Meckel's diverticulum; sclerosis of the ovaries; atrophy of the uterus; chronic cystic mastitis and atrophy of the breasts.

SUMMARY

The acromegaly in this case began at about the age of 24 years with the classical symptom of amenorrhea. The typical skeletal changes were far advanced and the field of vision was seriously impaired (the patient had only nasal vision in one eye) when the patient presented herself at the age of 33. She came mainly because of symptoms referable to diabetes which apparently had been of fairly recent origin. Pronounced pigmentary changes together with the characteristic broadening of the features combined to give this woman of French and Norwegian ancestry a definitely negroid appearance.

A transphenoidal decompression with partial hypophysectomy, followed by relatively small doses of roentgen-ray to the pituitary region, resulted in considerable improvement of vision, in disappearance of headache and night sweats and in diminution of the acromegalic myxedema, but had no effect on the diabetes or amenorrhea. For 6 years (between 1929 and 1935) during which time additional pituitary irradiation to the extent of 1750 r was administered, the progress of the acromegalic changes apparently was held in abeyance. However, the patient's course was complicated by a pulmonary abscess, one bout of diabetic acidosis and a diffusely disseminated xanthomatosis. During the following 3 years, from 1935 to 1938, the diabetes was well controlled but unmistakable signs of a slow but progressive enlargement and increased activity of the pituitary tumor appeared. Surgical treatment was recommended but refused by the patient. Therefore additional pituitary irradiation in the amount of 2600 r was administered. What effect this treatment may have had cannot be postulated since the patient terminated her own life.

Since exitus occurred only 17 days after the last

roentgen-ray treatment, this case afforded the rare opportunity of studying the histological effects of roentgen-rays on the human pituitary, or at least on an eosinophilic adenoma of the gland. Careful study of the sections showed that although there was evidence of edema and fibrosis, which were not apparent in the sections of the pituitary glands in the preceding cases, the histological changes attributable to roentgen-ray therapy were minimal and not indicative of therapeutic effectiveness.

An additional point of interest in this case is the early occurrence of amenorrhea which frequently is found in acromegalic women. This phenomenon is compatible with the presence of completely sclerotic ovaries and with atrophic breasts and uterus.

DISCUSSION AND CONCLUSIONS

Certain observations made in these 4 cases of acromegaly stand out in bold relief. All four patients came to an untimely death (at the age of 37, 45, 58 and 43, respectively). In each instance death was caused by the extension or degeneration of the pituitary tumor or by one of the numerous complications of acromegaly. Even the death of suicide may be attributed directly to the disease since life under this handicap was no longer endurable to the patient.

Were these untimely deaths avoidable? If so, how? The very characteristics of the disease, its insidious development, its rarity, its extremely chronic but cyclic course with spontaneous exacerbations and periods of inactivity, and its multiplicity of complications which sometimes overshadow the evidence of the primary disease, all contribute to the difficulty of the problem. How is the status of an acromegalic to be evaluated at any one point in the course of his malady? When is the disease active, when is it quiescent? When does the patient require treatment? When is 'watchful waiting' indicated? If signs of activity are present, what is the treatment of choice?

The dictum heretofore generally accepted was that surgical intervention is warranted only when vision is endangered or when life is threatened by signs of increasing intracranial pressure. These we shall call the neurological considerations. Hypophysectomy for endocrinological reasons alone is rarely done. Roentgen-ray therapy is the only alternative treatment. If the tumor is radio-sensitive, the response even to moderate dosage, as far as improvement of visual fields and headache are concerned, is likely to be prompt. But the dosage usually is insufficient to arrest the endocrine activity of the tumor. In other instances the tumor, inhibited temporarily by roentgen-ray, resumes its pathological activity in the course of time so that further treatment is required. The truth of this observation is demonstrated by the sections of the eosinophilic adenomas of the pituitaries in these four cases (fig. 4, *a*, 9, 12 and 16). All four patients had some roentgen-ray therapy; the first patient had four courses. Nevertheless, the microscopic picture of 3 of the pituitary adenomas was that of actively functioning tissue. The patient in *Case 4* received 2600 r to the pituitary only 3 weeks before death; although there was some evidence of fibrosis, the cytological picture still was that of a fairly active gland.

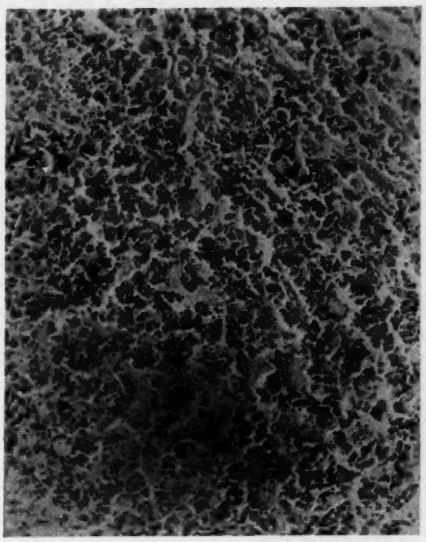

Fig. 16. EOSINOPHILIC ADENOMA of anterior hypophysis of *case 4*. Irradiation (2600 r), 3 weeks before suicide. Note edema and slight amount of fibrosis. ×85.

Besides the neurological findings and the alterations in sella turcica, visual fields and eye grounds, what are the criteria by which the intensity of the endocrine pathologic physiology can be evaluated? The most faithful observations of an acromegalic from month to month or from year to year may fail to impress one with the insidiously progressive changes in features and in the skeleton unless calibrated photographs are taken periodically for comparison. Careful follow-up records of head size, shoe and glove size and chest measurements should be made. Dental casts offer a better gauge of mandibular changes and separation of teeth than x-ray films. Alterations in the skull and sella turcica should be recorded by repeated roentgenograms at regular intervals. These are the methods of measuring the bony changes. Dare we wait, however, until these changes become measurable? They are irreversible. If we procrastinate we may lose the most favorable opportunity for prophylactic treatment. What are the signs and symptoms of 'acromegalism'?

In our experience, any acromegalic who has an increased basal metabolic rate, who shows lowered

carbohydrate tolerance with or without glycosuria, who has polydipsia, polyphagia, or both, and who complains of excessive perspiration or night sweats, probably is in the active progressive stage of the disease although signs of increased intracranial pressure, headache, visual disturbance and characteristic limitations in the visual fields may not have appeared. We do not mean to intimate that these symptoms constitute the sole evidence of activity or that activity may not be present without them. But until the blood hormone level produced by the eosinophilic adenoma of the pituitary can be assayed, these clinical findings may be utilized as guides in therapy.

Increased basal metabolic rate. Davidoff (2) in his report on a study of 100 cases from Cushing's series, noted an increased basal metabolic rate in 70 per cent of 70 cases. It is noteworthy that although enlargement of the thyroid frequently is observed (Davidoff found it in 25 per cent of the cases), it usually is of the colloid goiter type in which low cuboidal epithelium lines the acini. One of our patients who is undergoing treatment at the time of this writing illustrates this point very well. She is a 57-year-old woman who has had acromegaly for 9 years. Despite two thyroidectomies at the ages of 36 and 52 years, respectively, the basal metabolic rate at 57 years of age was still +30 per cent. Following pituitary irradiation alone, the rate fell promptly to normal. The thyroid tissue removed 6 years previously was reported to have been that of a colloid goiter.

Excessive perspiration. Davidoff (2) reported the occurrence of excessive perspiration in 60 per cent of his cases. This symptom, which occurs during periods of exacerbation and disappears or diminishes during the relatively quiescent periods, is another index of the degree of activity. In women, night sweats as a result of ovarian failure may complicate the picture. The response to estrogenic therapy may help to settle this point.

Polyphagia and gain in weight. Gain in weight due to increased food intake is likely to be one of the earliest symptoms of acromegaly. Because of its transient character it may easily be missed if the history is taken later in the course of the disease. Davidoff reported polyphagia in 28 per cent and gain in weight in 39 per cent of his series. The additional weight does not consist merely of increased fat but is due to an actual increment in body substance. Lee (11) reported that, in rats, injections of anterior pituitary growth hormone increased the appetite and the voluntary food consumption and promoted weight gain by greater deposition of proteins. Visceromegaly resulted; especially in the liver, hyperplasia of the tissue was evident. Furthermore, a decrease in excretion of urinary nitrogen occurred which was entirely due to a lowered output of urea; creatinine and uric acid excretion did not appear to be affected. In dogs which had received injections of anterior pituitary growth hormone Teel and Watkins reported a decrease in blood NPN. of 20 to 30 per cent. They interpreted this finding as an indication of increased nitrogen retention and synthesis of proteins due to the action of the growth hormone. Thannhauser and Curtius (12) found that endogenous catabolism was increased in acromegalic patients. Schrire and Sharpey-Schafer (13) reported increased excretion of creatinine with marked fluctuation in four acromegalics; treatment with estradiol benzoate in the female and with testosterone propionate in the male caused return to normal and cessation of the fluctuation. The excretion of creatin, which also had been excessive was not affected.

Hyperglycemia. Hyperglycemia, with or without glycosuria, in acromegaly is another index of the activity of the pituitary process. The incidence is given as ranging from 11 to 40 per cent. In Davidoff's series, the incidence of diabetes was 12 per cent and that of glycosuria 25 per cent. In our series of 4 cases, the incidence of diabetes was 75 per cent. At this point it is well to emphasize that statistics on this subject are unreliable since time is the incalculable factor. In one of our acromegalics (*case 1*) severe diabetes developed in the 17th year of the disease, 6 months prior to death. Had death overtaken this patient 6 months earlier, he would have been classified as an acromegalic without diabetes. On the other hand, in the second patient, the only one in our series who did not have this complication, diabetes may conceivably have developed during the last years of life when we did not observe him.

The question whether the mechanism for the production of diabetes in acromegaly is the same as that for pancreatic diabetes is beyond the scope of this discussion. The work of Houssay (14) and of Long and Lukens (15, 16), among others, suggests that a different mechanism may be at work. Further elucidation of the problem may change even our present concepts of ordinary diabetes mellitus. Suffice it to say that, for practical purposes, the treatment of acromegalic diabetes is the same as that of diabetes in general unless one or both of two complicating factors are encountered. These are *a*), increased insulin resistance and *b*) polyphagia, which, due to the acromegaly *per se* and not to the diabetes, make dietary management more difficult. On the other hand, improvement of impaired carbohydrate tolerance has been reported to have resulted from pituitary irradiation (17).

Therapy

In weighing the modes of treatment in acromegaly, we do not assume to lay down rules on basis of the

four cases described here, but we merely wish to point out some of the problems commonly encountered.

Roentgen-ray therapy. At the present time pituitary irradiation is the most effective form of therapy. Vaughan (18), reporting a series of 53 patients with acromegaly who were treated by pituitary irradiation, recommended 9 doses of 300 r each on successive days through 3 different portals. He observed as a result, prompt symptomatic relief of headache and visual impairment, cessation of polydipsia and polyuria, improvement of acromegalic myxedema and personality changes, as well as general improvement and a feeling of well being. He advised that if no improvement occurred the tumor should be considered radio-resistant but the treatment should nevertheless be repeated in 2 or 3 months. If, then, no remission is produced, the tumor should be considered as definitely radio-resistant. He warned that the total dose of 2700 r may be followed by a period of lethargy, lowered vitality and by a lowered basal metabolic rate; that the patient may become uncomfortable and susceptible to infections and complications, but that usually he returns to normal after 1 or 2 months. Armed with this knowledge, the patient, as well as his physician, may be saved unnecessary discouragement over the immediate results of pituitary irradiation. We believe, however, that the ultimate success of radiotherapy in acromegaly is achieved by application of repeated series of adequate dosage. One should not be content merely to relieve the headache and improve the visual fields; but one should exert every effort to control the endocrinopathic hyperactivity. Subsequently one should not wait until headache and visual disturbances have recurred before repeating irradiation. One should be ready to apply therapy at the first signs of increasing endocrine activity. Thus, the emphasis must be placed squarely on alert and scrutinizing follow-up. Since it is very easy to lose perspective in a disease of such long duration and such insidious course, one of us (*M. B. G.*) has devised a tabular chart for a periodic check-up of acromegalics (table 1).

Sex hormones. Marrian and Butler (19) showed that large doses of estrogen decreased pituitary activity while small doses might stimulate it. Kirklin and Wilder (20) and Schrire and Sharpey-Schafer (13) utilized this principle in the treatment of acromegaly. The latter workers used estradiol benzoate in women and testosterone propionate in men. We believe that these and related substances are valuable adjuvants to therapy when they are indicated. In our own experience two patients have been benefited by such treatment (21).

Surgical therapy. We deplore the laissez faire policy which characterizes the treatment of acromegalics in whom life or vision are not immediately threatened. Should not the surgical approach to this problem be considered more often in cases of young and early acromegalics to the end that such monstrosities as the patient in case 2 may be prevented? Surely, neurosurgery, with its ever-receding percentage of fatalities deserves a more prominent place in the treatment of acromegaly for endocrinopathic reasons alone, even when signs of increased intracranial pressure are absent. The sella turcica in this disease is greatly enlarged in the majority of cases and therefore is readily accessible to the expert neurosurgeon.

Strikingly illustrative of this argument is a recent experience of the authors, both of whom were called in consultation in the case of a 23-year-old girl whose

TABLE 1. PROGRESS CHART FOR ACROMEGALICS

Name: No.: Sex: S.M.W.D.
Date of Birth: Race: Occupation:
Date of Onset: Age: Earliest Symptoms:
Date First Seen: Age: Presenting Symptoms:

	Date	Date	Date	Date
Skeletal changes				
Headache				
Visual disturbances (subj. and obj.)				
Excessive sweating Night sweats				
Somnolence Lethargy, weakness				
Catanemia Libido Potentia				
Polyuria Polydipsia				
Polyphagia				
Weight				
Pulse Blood pressure				
Urinalysis				
Blood sugar Blood sugar tolerance				
Blood chemistry				
B.M.R.				
Photographs				
Dental casts				
Therapy Surgery X-Ray Other				
Remarks				

acromegaly was complicated by diabetes mellitus, renal impairment, malignant hypertension, tachycardia, goiter, increased basal metabolic rate, amenorrhea, heterosexual hypertrichosis and somewhat enlarged clitoris. Even before the age of 20 years this girl had had some limitation of the visual fields which seemingly was corrected by pituitary irradiation. Nevertheless, when she was 21 years old, one of us (*H. L.*) considered the acromegaly in this patient to be in a progressive hyperactive state and urged subtotal hypophysectomy because postponement of such radical therapy involved the greater hazard of a more

TABLE 2. ANTHROPOMETRIC MEASUREMENTS OF CASE 1

Taken August 14, 1928	Patient's age, 28 yr.
Weight	192 lb.
Height, standing	167.7 cm.
sitting	92.0 cm.
Chest, circumference	103.8 cm.
breadth (transverse)	32.4 cm.
depth	27.6 cm.
Shoulder, biacromial	40.6 cm.
Pelvis, bicristal	29.8 cm.
Head, length	19.7 cm.
breadth	15.9 cm.
ear height	12.9 cm.
face length	12.7 cm.
face breadth	15.8 cm.
nose length	5.2 cm.
nose breadth	4.7 cm.
Hand, length	18.8 cm.
breadth	9.8 cm.

dangerous condition later. The patient and her family refused operation. A year later radiation therapy was again attempted but two courses proved ineffectual. Three months after the last treatment surgical intervention became imperative because of sudden and severe visual impairment. The patient died 12 hours postoperatively from respiratory failure due to uncontrollable edema of the brain. Therapy in this case had been too little and too late.

In conclusion, therefore, we urge consideration of a more radical attitude toward partial hypophysectomy at least in those patients who have not responded completely to adequate pituitary irradiation. This recommendation is based on the same thesis as that which justifies removal of a parathyroid adenoma for osteitis fibrosa cystica (hyperparathyroidism), of an islet cell tumor for hyperinsulinism, of a pheochromocytoma for paroxysmal hypertension, of adrenal cortical tumors which cause sexual precocity or masculinization, of granulosa cell tumors, of arrhenoblastoma and finally, subtotal removal of the

TABLE 3. ANTHROPOMETRIC MEASUREMENTS OF CASE 2

	August 7, 1928	July 25, 1936 (postmortem)
Weight	268 lb.	265 lb. ±
Height, standing	178.2 cm.	188 cm.
sitting	94.0 cm.	
Head, occipital frontal circumference		62.9 cm.
occipito-supraorbital circumference		87.3 cm.
bregma mental		78.2 cm.
length	21.9 cm.	25.4 cm.
breadth	16.3 cm.	
ear height	13.7 cm.	
Face, length	16.5 cm.	
breadth	16.1 cm.	
Nose, length	6.8 cm.	
breadth	5.0 cm.	
Neck		43.2 cm.
Thorax, circumference at 4th costosternal junction	120.0 cm.	112.0 cm.
7th		117.5 cm.
10th		116.2 cm.
breadth (transverse)	36.8 cm.	
depth (AP) (unsatisfactory)	33.7 cm.	
Torso, length—acromion to AS spine		57.8 cm.
7th cervicle to tip of coccyx		66.0 cm.
circumference at level of trochanters		112.0 cm.
Shoulder, bi-acromion	42.2 cm.	
Arms, length, acromion to tip of 2nd finger		88.8 cm.
acromion to olecranon		40.4 cm.
olecranon to styloid of ulna		32.8 cm.
circumference of biceps		30.5 cm.
of forearm		24.1 cm.
Hands, greatest length, dorsal	21.4 cm.	21.5 cm.
palmar		18.4 cm.
circumference, heads of metacarpals		27.9 cm.
thumb at first phalanx		9.5 cm.
1st finger		9.5 cm.
2nd finger		9.5 cm.
3rd finger		9.2 cm.
4th finger		9.0 cm.
at wrist		21.9 cm.
breadth	11.2 cm.	
Pelvis, bi-trochanteric	37.0 cm.	
Legs, circumference, mid-thigh		49.0 cm.
calf		34.7 cm.
malleolus		29.2 cm.
length—AS spine to tip of 1st toe		108.0 cm.
trochanter to head of fibula		38.8 cm.
Feet, length, heel to top of first toe		29.0 cm.
circumference, mid tarsal		27.3 cm.
heads of metatarsals		27.3 cm.
great toe		12.0 cm.

thyroid for hyperthyroidism. Radical reduction or excision of the hyperfunctioning tissue constitutes the most logical and the most direct approach. The risks involved are not excessive as compared to the hideous deformities and dangerous complications which almost always eventuate in neglected acromegalics. Of this disease it may truly be said, 'Time marches on.'

We are indebted to Dr. Robert Stone and Dr. J. Williams, roentgenologists, for their aid in reporting the details of technique and dosage of pituitary irradiation. We gratefully acknowledge the opportunity to report the pathological findings in autopsies performed by Dr. Charles Connor (deceased), Dr. Jesse Carr, and Dr. C. E. Smith and Dr. Dale Barbour as well as the Department of Pathology, Stanford University Medical School (*case 3*). We appreciate the advice and cooperation of Dr. Howard Naffziger and his associates of the Department of Neurosurgery (*case 2*).

ADDENDA

The following statistical information is added for the benefit of those readers who may be especially interested.

Synopsis of Roentgen-ray Therapy

Case 1: In 1923 the patient received a course of pituitary irradiation the amount of which is impossible to determine but which apparently did not produce epilation. Between June 4 and July 8, 1929, he received 2 treatments to each temporal region on a 120 K.V. apparatus, directed at a field 12×12 cm. Apparently 250 r were administered to each side of the head. In 1931 treatment was given on a 200 K.V. apparatus with a filter of 0.5 mm. Cu and 1 mm. Al at a 50 cm. focus-skin distance over an area 4 cm. in diameter. Twelve treatments were given at weekly intervals, 6 to the right and 6 to the left temporal region, or a total of 1050 r to each side. Between Dec. 13, 1933, and June 7, 1934, he received 18 treatments with rotation through 3 portals, the right temporal, the left temporal and the anterior. A 200 K.V. apparatus was used with a filter of 0.2 mm. Sn, 0.25 mm. Cu and 1 mm. Al at a 50 cm. skin target distance. The area irradiated was 6×6 cm. In all 1200 r were given through each portal, or a total of 3600 r.

Case 2: The patient was treated to the right side of his head, aiming at the pituitary, on July 20 and on Aug. 21, and to the left side of his head, aiming at the pituitary, on July 31 and on Aug. 28, 1923. It is impossible to estimate the number of roentgens administered during the treatments given in 1923. A 10-inch spark gap apparatus was said to have been used. The filter was 0.5 mm. Cu and 1 mm. Al. The distance of the target was 14 in. On July 20, 280 milliampere-minutes were given; on July 31, about 400; on Aug, 21, 300; and on Aug, 28, 420. The closest estimate of the dosage would be 15 r to every 10 milliampere-minutes.

Case 3: The patient received 4 treatments of 200 r each to the right and left temporal regions on June 20, 24, 28 and Aug. 20, 1935. A 200 K.V. apparatus was used with a filter of 0.5 mm. Cu and 1 mm. Al. The focus-skin distance was 40 cm. and the area irradiated was 9 cm. in diameter. The total dose was 800 r (in air) to each temporal area.

Case 4: The patient first received roentgen-ray treatment in 1928. On Nov. 2 and 7, she was treated to the left side of the head aiming at the pituitary and on Nov. 5 and 9, to the right side of the head aiming at the pituitary. On each occasion she received 150 milliampere-minutes with an apparatus running at 120 K.V. The radiation was filtered through 0.25 mm. Cu and 1 mm. Al. The distance of the skin target was 15 in. Calculating from our present knowledge, we would say that between Nov. 2 and 9, 1928, the patient received about 350 r at each treatment, or a total of 700 r to the left and 700 r to the right side.

The patient was again treated in November, 1929, at which time the same fractions were given. Similar treatments were administered between Nov. 1 and 11, with the exception that 3 treatments were given to the left (Nov. 1, 6 and 11) and 2 to the right side (Nov. 4 and 6).

In 1938 most of the treatment was given on the 1000 K.V. apparatus with filtration of 2 mm. of lead. The treatments were rotated through from the right lateral, the left lateral and the anterior portals, so that between April 21 and May 4 the patient received treatment almost every day, the amount being 850 r (in air) to the left side and to the anterior field and 900 r to the right lateral field.

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Carbohydrate Metabolism of Animals Treated with Methyl Testosterone and Testosterone Propionate[1]

[Androgens and Carbohydrate Metabolism]

LENA A. LEWIS, PH.D. AND
E. PERRY MCCULLAGH, M.D.

From the Cleveland Clinic, Cleveland Ohio

THAT THE USE of methyl testosterone in patients is followed by a decrease in tolerance for glucose has been reported (1). In an attempt to explain the mechanism involved, studies have been extended to rabbits. Glucose tolerance and liver and muscle glycogen have been determined when no treatment has been given, and when methyl testosterone and testosterone propionate have been administered. The fact that there is a marked increase in the basal metabolic rate of the animal treated with methyl testosterone suggested that the hypermetabolism itself might be affecting the glucose tolerance in a manner similar to that operative in hyperthyroidism. To study this, determinations were made of the glucose tolerance of thyroidectomized rabbits before and after treatment with methyl testosterone. Rats were also treated with methyl testosterone and the values for liver glycogen compared with those in normal controls. Similarly, the liver glycogen of hypophysectomized rats without treatment and with methyl testosterone therapy were compared.

EXPERIMENTAL METHODS

Rabbits; normal animals. Adult male rabbits ranging in weight from 2.7 to 3.5 kg. were used. They were fed a constant diet of oats, hay, and carrots. Water was allowed ad libitum. The food was withheld for 24 hours before the beginning of a test period. Glucose tolerance was determined. Seven and one-half gm. of glucose dissolved in 35 cc. of water was given by stomach tube for the oral tests. Fifteen cc. of a 50 per cent glucose solution was injected for the intravenous tests. Blood samples were collected from the ear vein 0, 0.5, 1, 2, 3, and 4 hours after the administration of glucose. Blood glucose was determined using the Somogyi modification of the micro-Shaffer-Hartmann method (2). The urine excreted during the test period was collected and tested for glucose. If any was present, a quantitative determination using the quantitative Benedict's reagent was made (2b).

Methyl testosterone was administered orally, daily in doses of 5, 10, or 20 mg. The rabbits receiving the testosterone propionate were injected daily with 5, 7.5, or 10 mg. of the hormone dissolved in sesame oil. The sugar tolerance curves were determined from time to time during the period of treatment. When no further modification in the curve occurred, the animals were killed, and the liver and muscle glycogen content were determined (3). The rabbits were placed under nembutal anesthesia, the gastrocnemius muscle was dissected out as rapidly as possible and immediately frozen in dry ice. The liver was quickly exposed and representative sections from each lobe were dropped into 30 per cent KOH solution. The testes, seminal vesicles, prostate, adrenals, pituitary, and a piece of pancreas, liver, and kidney were saved for histological study. Normal untreated rabbits which had been on the standard diet for at least 4 weeks were used for normal control glycogen determinations.

Thyroidectomized animals. Rabbits were thyroidectomized under nembutal anesthesia. Following operation they were injected with 10 units of parathormone and were given 5 grains of calcium lactate and 50 units of vitamin D daily. After two weeks the parathormone was discontinued, but the other treatment was given throughout the experimental period.

Rats. A group of 22 normal male rats 104 days of age and of approximately the same body weight was selected. They were fed a constant diet of Purina dog chow, bread, and lettuce. Eleven of the animals were given 5 mg. of methyl testosterone per day orally and 11 were used as controls. After 38 days of treatment they were killed 24 hours after withdrawal of food, and the liver glycogen levels were determined. Two groups of male rats were hypophysectomized.

Received for publication July 2, 1942.

[1] Read before the American Physiological Society, April 3, 1942, Boston, Mass.

TABLE 1. SUGAR TOLERANCE OF RABBIT 6, TREATED WITH METHYL TESTOSTERONE

Date	Days of Treatment with 10 mg. Methyl Testosterone	Body Weight, kg.	Dextrose, Given, 7.5 gm.	Urine Glucose, gm.	Blood Sugar, mg/100 cc.					
					Fasting	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.
7/10/41	0	2.88	Orally	0	92	149	174	166	124	107
7/14/41	0	2.85	Orally	0	100	141	174	162	115	115
7/31/41	8		Orally	0	100	141	166	149	107	107
8/ 7/41	15	2.84	Orally	0	107	182	190	153	107	100
8/14/41	22		Orally	0	100	198	224	174	132	100
8/21/41	29	2.81	Orally	0	107	190	215	174	141	100
9/ 3/41	42	2.82	Orally	0	100	190	207	174	149	107
7/17/41	0	2.88	Intravenously	1.8	100	524	321	124	100	83
7/21/41	0		Intravenously	1.8	97	518	330	127	88	97
8/27/41	35	2.83	Intravenously	2.16	100	487	380	157	115	107

The first group was 152 days of age at operation, and the second group was 88 days old. Half of each group was given 5 mg. of methyl testosterone per day, starting the second day after operation; half received no treatment and were used as controls. Thirty days after operation they were killed 10 hours after withdrawal of food, and liver glycogen values were determined. Each animal was checked for completeness of hypophysectomy; the testes were weighed.

RESULTS

Rabbits. Following 22 days of treatment with 10 mg. of methyl testosterone daily, the sugar tolerance curve in the rabbit showed a definite deviation from normal. The level to which the blood sugar rose was increased, and the return to normal was prolonged. A modification in the curves following both the oral and intravenous administration was observed. After 15 days a questionable deviation from normal was observed. After 29 days the maximum variation was established, and further treatment for as long as 45 days produced no additional effect. Table 1 gives the data on *rabbit* 6 and are typical of that observed in the other 8 rabbits similarly treated. The dosage of methyl testosterone appeared to play little part in the time of onset of the change in sugar tolerance. Rabbits receiving 10 mg. per day showed a modified tolerance at about the same time as those receiving 20 mg. per day. Two of the 3 animals receiving 5 mg. per day showed a modified curve in 29 days, whereas the third showed no significant change until after 36 days of treatment.

In 6 animals, after extensive treatment with methyl testosterone and after a maximum change had been observed in the sugar tolerance, additional carbohydrate (15 gm. sugar per day) was included in the diet. One week later the sugar tolerance curves were found to be within normal limits. In these animals, as in other animals with depleted glycogen stores, there appeared to be a diminution in glucose tolerance. Provided with additional carbohydrate, the animal was able to restore the glycogen stores to normal levels. Figure 2 shows the glycogen values in the 3 animals killed at this time. Two weeks after the withdrawal of the extra carbohydrate, the 3 rabbits again showed a decreased tolerance (table 2).

TABLE 2. BLOOD GLUCOSE VALUES IN RABBIT 15 RECEIVING METHYL TESTOSTERONE AND HIGH CARBOHYDRATE DIET

Date	Treatment	Glucose, mg. per 100 cc. of Blood					
		Fasting (after 7.5 gm. glucose)	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.
10/ 3/41	None	83	174	194	149	122	100
10/24/41	None	92	182	182	149	107	83
12/23/41	Methyl test, 5 mg. per day, 39 days	92	188	215	169	141	115
1/29/42	Methyl test, 5 mg. per day, 69 days. Last 14 days given 15 gm. additional carbohydrate in diet	92	190	190	149	107	96
1/30/42	Added carbohydrates withdrawn from diet						
2/19/42	Methyl test, 5 mg. per day, 90 days	83	188	207	166	141	107

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Treatment with testosterone propionate, on the other hand, did not significantly modify the sugar tolerance curves of the treated rabbits. Treatment for as long as 55 days with 10 mg. of testosterone propionate per day was ineffective in modifying the testosterone to maintain a normal liver glycogen.

The muscle glycogen level of neither the animals treated with testosterone propionate, or methyl testosterone, nor those receiving the methyl testosterone and high carbohydrate diet was significantly

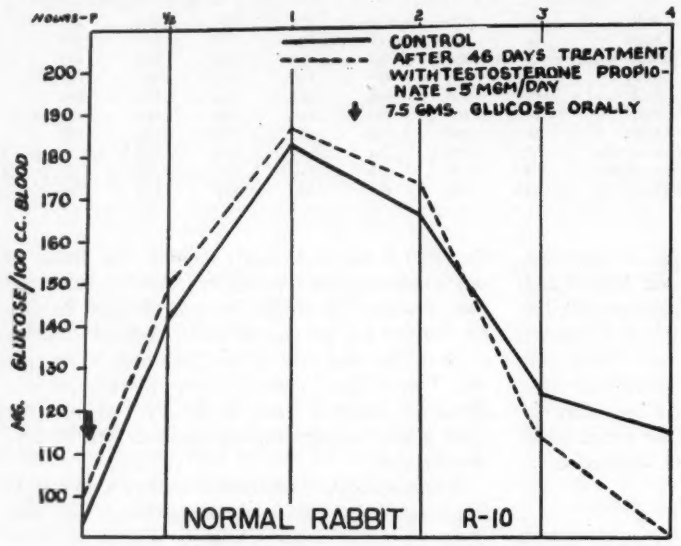

Fig. 1. Blood sugar curves of a normal rabbit before and after treatment with testosterone propionate.

tolerance for glucose. Figure 1 shows the results obtained on R10 and is typical of the values obtained on the 5 rabbits thus treated.

The rabbits receiving methyl testosterone and testosterone propionate showed no increase in body weight. A gain in weight, caused chiefly by retention of fluid, frequently is observed in the human being receiving large amounts of these hormones.

Figure 2 shows the liver and muscle glycogen values of the normal rabbits and of the animals receiving treatment with methyl testosterone and testosterone propionate. The average control level of liver glycogen was 0.568 gm. per cent, the range being from 0.445 to 0.740 gm. per cent. In the animals treated with methyl testosterone the average liver glycogen was 0.338 gm. per cent, the range being from 0.242 to 0.417 gm. per cent. In the animals treated with testosterone propionate the average liver glycogen was 0.757 gm. per cent, the range being from 0.611 to 0.840 gm. per cent. In the animals receiving methyl testosterone and a high carbohydrate diet, the average liver glycogen was 0.650 gm. per cent, the range being from 0.532 to 0.800 gm. per cent. The level of liver glycogen thus was markedly decreased following prolonged treatment with methyl testosterone and was somewhat increased following testosterone propionate treatment. A high carbohydrate diet enabled the animal treated with methyl

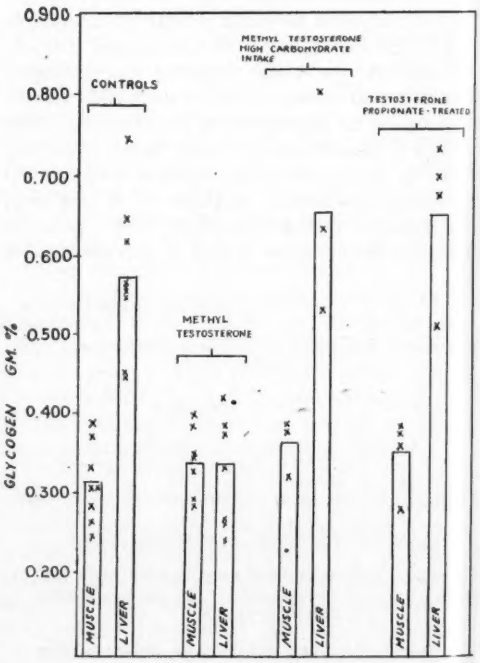

Fig. 2. Muscle and liver glycogen of rabbits treated and untreated with methyl testosterone.

altered from the normal. The average control level of muscle glycogen was 0.311 gm. per cent (range 0.248 to 0.385 gm. per cent). The average for the animals treated with methyl testosterone was 0.338 (range 0.283 to 0.387) gm. per cent; that for the animals receiving methyl testosterone and a high carbohydrate diet was 0.36 (range 0.322 to 0.380) gm. per cent; and that for the group treated with testosterone propionate was 0.351 (range 0.284 to 0.384) gm. per cent.

Thyroidectomized animals. The studies of glucose tolerance of the thyroidectomized rabbits were started 5 weeks after operation. After oral and intravenous tolerance curves had been determined, treatment with methyl testosterone was instituted. Figure 3 summarizes the results obtained on *R18*, one of the 3 animals thus treated. Any modification in the glucose tolerance of the thyroidectomized animal following methyl testosterone treatment was very slight, and the period of treatment before the questionable change was much longer than that required for maximum change in the normal animal treated with methyl testosterone.

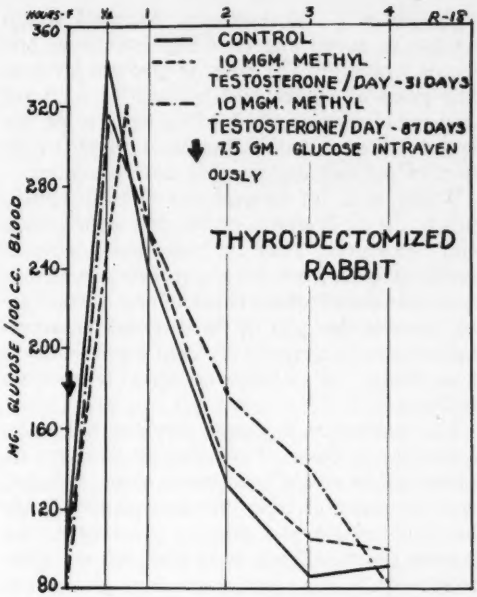

Fig. 3. Blood sugar curves of a thyroidectomized rabbit before and after treatment with methyl testosterone.

Table 3. Effect of Methyl testosterone on liver glycogen of normal and hypophysectomized rats

Rat No.	Age at Operation or Beginning of Experiment, days	Treatment	Liver Glycogen, gm. %	Testes Weight, gm.
1	104	None	.252	2.9
2	104	None	.380	2.9
3	104	None	.232	2.8
4	104	None	.346	2.2
5	104	None	.330	2.4
6	104	None	.378	2.8
7	104	None	.298	2.3
8	104	None	.320	2.6
9	104	None	.216	2.0
10	104	None	.274	2.5
11	104	None	.342	2.8
Average			.306	2.57
1-T	104	5 mg. meth. testost.	.247	1.4
2-T	104	/ day	.221	1.5
3-T	104	38 days	.211	1.5
4-T	104	38 days	.194	1.6
5-T	104	38 days	.245	1.5
6-T	104	38 days	.190	1.0
7-T	104	38 days	.218	1.9
8-T	104	38 days	.144	1.9
9-T	104	38 days	.220	1.5
10-T	104	38 days	.236	1.7
11-T	104	38 days	.123	1.7
Average			.209	1.56
2-0	88	hypophysectomized	1.38	1.1
6-0	88	hypophysectomized	1.46	0.5
4-0	88	hypophx.-methyl test.	1.62	0.9
5-0	88	hypophx.-methyl test.	1.48	1.0
7-0	88	hypophx.-methyl test.	1.33	0.9
3-0	88	incomplete hypophx.	2.36	2.2
9-0	152	hypophysectomized	1.38	0.5
10-0	152	hypophysectomized	.88	0.4
11-0	152	hypophysectomized	1.40	0.7
14-0	152	hypophysectomized	1.63	0.8
15-0	152	hypophysectomized	1.55	0.6
8-0	152	hypophx.-methyl test.	1.18	0.7
13-0	152	hypophx.-methyl test.	0.80	1.0
12-0	152	incomplete hypophx.	1.78	2.6
16-0	152	incomplete hypophx.	2.46	2.9

Rats. Table 3 summarizes the results on the unoperated rats and the hypophysectomized animals. In the unoperated group a decrease in liver glycogen was observed following hormone administration which was similar to that observed in the rabbits treated with methyl testosterone. In the operated groups the range of liver glycogen levels was so great that definite conclusions could not be drawn. However, there appeared to be no significant variation between the untreated operated animals and the group treated with methyl testosterone.

DISCUSSION

The fact that no significant change in the muscle glycogen of the rabbits was observed following treatment with testosterone propionate is in agreement with the findings of Gaunt et al. (4) in rats. However, they observed no significant modification in the liver glycogen. That our animals received treatment for a very much longer period may account for the difference. Although the slight increase found by us appears to be statistically significant, the change is small in comparison with that produced by cortical extract and some other hormone preparations.

Cahone et al. (5) reported a decreased muscle glycogen in guinea pigs following testosterone propionate treatment. The range of glycogen levels in their group of control animals (0.938 to 5.372 per cent) and of treated animals (0.764 to 4.509 gm. per cent) was so great that the decrease, as judged by the means of 3.11 and 2.04, probably is not significant.

Winter et al. (6) reported that phlorhizin glycosuria in the rat is greatly inhibited by pretreatment with testosterone. They attributed the decrease in glycosuria to the protective action of the testosterone on the convoluted tubules of the kidney. It would appear possible that part of the decreased glycosuria might be due to decreased glycogen stores similar to those observed by us following methyl testosterone treatment.

The modification in glucose tolerance and carbohydrate storage observed following the prolonged administration of methyl testosterone seems to depend upon the action of other endocrine glands. In the absence of the thyroid or pituitary gland the changes were not observed. There is no proof that the whole modification is dependent upon these glands, and other mechanisms may also be involved. The fact that the animal treated with methyl testosterone was able to maintain normal carbohydrate stores and showed a normal glucose tolerance if greatly increased amounts of carbohydrate were given in the diet would indicate that the disturbance was due to increased utilization rather than to an inability to store carbohydrate.

SUMMARY

The glucose tolerance of rabbits was decreased following prolonged treatment with large doses of methyl testosterone. No modification in glucose tolerance was observed following a similar period of treatment with testosterone propionate. Thyroidectomized animals showed no apparent modification or a very slight decrease in sugar tolerance following prolonged treatment with methyl testosterone.

The level of liver glycogen of rabbits treated with methyl testosterone, and showing a modified sugar tolerance, was well below that of untreated normal controls. Following testosterone propionate treatment the liver glycogen was slightly but significantly increased. The muscle glycogen of neither group of treated animals was altered significantly.

The liver glycogen of rats treated with methyl testosterone was lower than that of untreated controls. There appeared to be no significant difference between the liver glycogen level of hypophysectomized untreated rats and hypophysectomized rats receiving methyl testosterone.

In the absence of the thyroid or pituitary gland, no modification in glucose tolerance or carbohydrate storage was observed following prolonged administration of methyl testosterone.

We wish to thank Dr. Max Gilbert of the Schering Corp., Bloomfield, N. J., for the methyl testosterone and testosterone propionate used in these experiments.

We are indebted to Dr. Owen Reeves for hypophysectomizing the rats.

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Carbohydrate Metabolism of Patients Treated with Methyl Testosterone

[Hypogonadism]

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That treatment of patients with large doses of methyl testosterone for long periods of time results in a modification of sugar tolerance has been reported (1). Studies have been extended to determine the factors involved in producing this change. In rabbits treated with methyl testosterone a decreased sugar tolerance also has been observed. The liver glycogen of these animals was less than that of untreated controls (2). In an attempt to determine whether a modification in liver glycogen reserves occurs in the human being receiving methyl testosterone, estimations using the phlorhizin technic of Mirsky (3) have been made. The test is based on the assumption that, following phlorhizin, 'when the blood-sugar level remains constant, all of the urinary sugar must have come from the liver. On the other hand, if there has been a fall in the blood-sugar level, then the amount of sugar excreted in the urine is equal to the sum of that secreted by the liver plus the sugar equivalent to the decrease in the blood and tissues' (3). The basal metabolic rate and the glucose tolerance of the patients treated with methyl testosterone also were determined. Generally, the basal metabolic rate was markedly above the pretreatment level when the decrease in sugar tolerance was observed, and the amount of glucose of liver origin excreted following phlorhizin usually was decreased.

Methods and Materials

Eight cases of male hypogonadism were studied before any treatment was given (or during a period of withdrawal of therapy), and during treatment with large doses of methyl testosterone. Sugar tolerance curves were determined following the oral administration of 100 gm. of dextrose. In the sugar tolerance tests the blood sugar values were determined by the method of Myers and Bailey (4). Basal metabolic rates were measured using the Sanborn-Grafic machine and the Mayo Clinic tables. Each test represented two runs. The hepatic glycogen reserves were measured by the phlorhizin method of Mirsky (3). Blood sugars were determined on venous blood by the Somogyi modification of the micro-Shaffer-Hartmann method (5). Blood acetone was determined by the method of van Slyke and Fitz (6, 7). Urinary nitrogen was determined by the Kjeldahl method (8). In some cases, when the patient was receiving methyl testosterone therapy, a diet high in carbohydrates was given to determine its effect upon the sugar tolerance and glycogen reserves during hormone treatment. The high carbohydrate diet consisted of 500 gm. of carbohydrate with a total caloric value of 3000 calories.

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Results

In some cases the administration of large doses of methyl testosterone was followed by a marked decrease in sugar tolerance. The decreased tolerance was usually associated with an increased basal metabolic rate. Table 1 summarizes the results on 7 of the patients.

Phlorhizin tests were made on 5 patients, the data on 4 of whom are included in table 1. Figure 1 summarizes the results on *patient 4*. Following treatment with methyl testosterone, the liver glycogen stores were 380 mg. per kg. of body weight. Upon withdrawal of therapy, they were 417 mg. per kg. of body weight or greater. As there was no drop in the blood glucose level, the amount of glycogen remaining in the liver at the end of the test was not indicated. With methyl testosterone therapy and an increased amount of carbohydrate in the diet, the liver glycogen stores were 464 mg. per kg. At the end of the 6-hour phlorhizin test, when the glycogen stores were lowest the blood acetone showed an increase of 100 per cent. Acetone was present in the 5th and 6th-hour urine specimens. The blood acetone was not significantly altered when no therapy was being taken or when a high carbohydrate diet was being ingested.

The glycogen storage values were based on the following points. The blood-sugar level did not drop during the 6-hour phlorhizin test period when the patient had been receiving no therapy, or when the patient was on the high carbohydrate diet—methyl testosterone regimen. The blood sugar values fell 13 mg. during the 6-hour test period when the patient was receiving methyl testosterone therapy. Employing the 30 per cent figure for the mixing volume for 80 mg. daily the second month), he showed a markedly decreased sugar tolerance. At that time, following phlorhizin injection, he excreted 537 mg. glucose per kg. of body weight, of which 490 mg. was of liver origin. The blood acetone was increased by 53 per cent at the end of the 6-hour phlorhizin test. Five months later on the same therapy, the sugar tolerance was more normal (fig. 3). At that time, following phlorhizin 521 mg. of glucose per kg. of body weight,

TABLE 1. EFFECT OF METHYL TESTOSTERONE ON BLOOD GLUCOSE LEVELS IN HYPOGONADAL MEN

Case	Diagnosis	Treatment		B. M. R. %	Sugar Tolerance, Glucose, mg./100 cc. at Hours					
		Duration, days	Methyl testosterone per day, mg.		0	½	1	2	3	4
1	Hypogonadism	30	0	−13						
		30	0	+ 3	97	122	130	98	104	
		19	300 mg.	+ 2	118	224	213	241	161	120
2	Hypogonadism	35	0	−11						
		42	0		104	207	127	94	76	
		19	300 mg.	− 3	109	213	187	200	125	
3	Hypogonadism	60	0	−17	102	102	90	80	78	
		60	100 mg.	+ 3	98	122	122	94	102	84
4	Hypogonadism	15	0	− 1						
		18	100 mg.		96	160	210	168	68	58
		120	60 mg.	+24	110	169	242	212	100	108
5	Hypogonadism	39	0	+ 1	102	116	90	108	78	
		49	250 mg.	+27	130	190	168	173	130	79
6	Hypogonadism	No previous treatment		−13	106	136	174	106	80	70
		21	100 mg.							
		42	200 mg.							
		30	300 mg.	± 0	106	155	132	147	93	85
7	Hypogonadism	30	100 mg.							
		21	200 mg.							
		21	300 mg.	− 3	106	171	238	204	117	77
		27	0	− 3	138	202	187	143	82	82

sugar distribution in the body, as used by Mirsky, 3.78 gm. of the sugar excreted was from non-liver source. The increase in blood acetone was also of significance.

Patient 3 excreted 488 mg. of glucose per kg. of body weight, all of liver origin, when no therapy had been taken for 3.5 months. The blood acetone was unaltered at the end of the test period. When he had received 100 mg. of methyl testosterone per day for two months, 470 mg. glucose per kg. of body weight was excreted, of which 413 mg. was of liver origin (fig. 2). At the end of the 6-hour phlorhizin test the blood acetone had increased from 1.6 to 3.5 mg. per 100 cc. of blood.

When *patient* 5 had been receiving methyl testosterone for 2 months (70 mg. daily the first month, all of which was of liver origin, was excreted following phlorhizin injection. The blood acetone was not significantly modified at the end of the 6-hour test period.

In the case of *patient* 8, who had been receiving 50 mg. of testosterone propionate 3 times a week for 4 months, 353 mg. of glucose per kg. of body weight, all of which was of liver origin, was excreted following phlorhizin injection. The blood acetone was not increased at the end of the 6-hour test period. After he had been receiving methyl testosterone (100 mg. per day for 5 months), the glucose excretion following phlorhizin was 422 mg. per kg. of body weight, the source of which was the liver. At that time he showed a slightly modified glucose tolerance curve. The blood acetone was not significantly altered.

When therapy was withdrawn for two months, 316 mg. of glucose per kg. of body weight was excreted. All was of liver origin. There was no significant modification in blood acetone at the end of the 6-hour test.

Patient 6 excreted 381 mg. of glucose per kg. of body weight following phlorhizin when he had received no treatment. All of this was of liver origin. After 3 months of treatment with methyl testosterone (100 mg. daily for 21 days, 200 mg. daily for 42 days, and 300 mg. daily for the 30 days immediately preceding the phlorhizin test) 365 mg. of glucose per kg. was excreted following phlorhizin, of which 318 mg. was of liver origin. In the first test no acetone was present in any urine specimen. In the phlorhizin test following methyl testosterone treatment the urine showed acetone in the specimens collected for the 4th, 5th, and 6th hours after the initial injection.

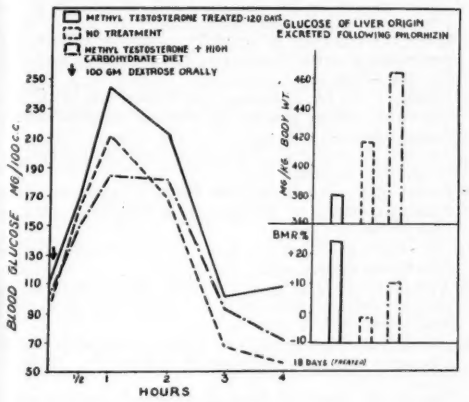

Fig. 1

Patient 7 excreted 221 mg. of glucose per kg. of body weight, which was of liver origin, after he had been receiving large doses of methyl testosterone for 10 weeks. The blood acetone was increased from 1.5 to 5.5 mg. per 100 cc. at the end of the 6-hour phlorhizin test. The hippuric-acid liver-function test at this time showed 3.0 gm. of benzoic acid synthesized (equivalent to 100 per cent of normal). After therapy had been withdrawn for 27 days, 245 mg. of glucose per kg. of body weight, which was of liver origin, was excreted. The blood acetone was 1.7 mg. per 100 cc. of blood at the beginning of the 6-hour phlorhizin test and 2.1 mg. at the conclusion of the test period.

Urine nitrogen was determined on aliquots of the pooled urine collected during the first 3 hours of the phlorhizin test period and the second 3 hours of the test. In no case was the nitrogen excretion significantly different in the two periods. This indicated that gluconeogenesis was not increased.

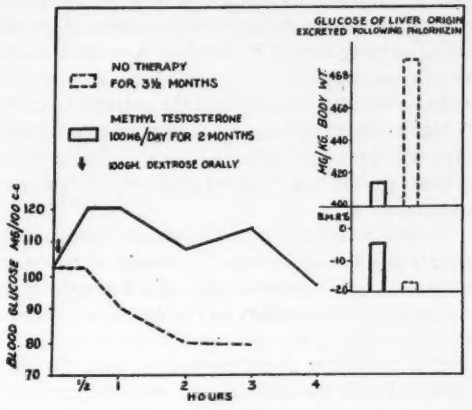

Fig. 2

DISCUSSION

The estimation of liver glycogen reserves, using the glucose excretion following phlorhizin as the basis of calculation, is open to certain fundamental criticism. Although the values thus estimated may not be the true ones, it is believed that repeated tests on the same individual are capable of showing actual changes in glycogen stores. It is also believed that greater significance can be placed on the decreased glycogen stores in patients following the use of methyl testosterone, since this change has been observed in treated animals in which the livers have been removed and glycogen values actually determined (2).

Winter et al. (9) reported that phlorhizin glycosuria in the rat is greatly inhibited by pretreatment with testosterone. They attributed this decrease to a modification in the epithelial cells lining the convoluted tubules of the kidney. No liver glycogen determinations were made on the testosterone-treated rats.

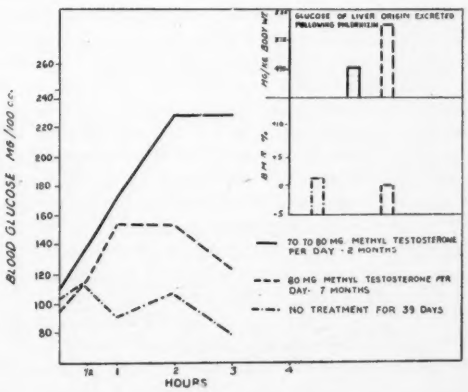
GLUCOSE OF LIVER ORIGIN EXCRETED FOLLOWING PHLORHIZIN
BLOOD GLUCOSE MG/100 CC.
MG/KG BODY WT
BMR %
70 TO 80 MG. METHYL TESTOSTERONE PER DAY - 2 MONTHS
80 MG METHYL TESTOSTERONE PER DAY - 7 MONTHS
NO TREATMENT FOR 39 DAYS
HOURS

Fig. 3

That the action of methyl testosterone on the kidney was responsible for the decreased excretion of glucose per kg. of body weight, of liver origin, seems unlikely, for in some cases the actual total excretion of glucose was as great in the treated as in the untreated patient. A significant percentage of it, however, originated from the blood and body fluids, as a marked decrease in blood glucose was observed at the end of the 6-hour test period.

In the case of *patient 5* it is difficult to explain the greater sugar tolerance after 7 months of treatment with methyl testosterone than after 2 months. Some compensatory mechanism may have become effective in the interval. The importance of the nature of the diet in modifying sugar tolerance cannot be disregarded. While the patients were not on a controlled diet, they were questioned as to any change in eating habits or food intake. This patient was unaware of any such change.

The unusually low glycogen reserves in *patient 7* are difficult to interpret. He was accustomed to eating unusually large amounts, and his diet represented a very large total carbohydrate intake. The food intake was essentially constant throughout the period of observation.

The results on *patient 8* cannot be evaluated to indicate change in glycogen stores, for at no time were the reserves exhausted following phlorhizin, as indicated by the maintained blood-sugar level and the absence of increased blood acetone.

The decreased glycogen reserves during methyl testosterone treatment could not be attributed to liver damage, for there was no evidence of decreased liver function, as judged clinically or by hippuric acid and bromsulfalein liver function tests.

SUMMARY

Following continued treatment with methyl testosterone, some patients showed a decreased sugar tolerance. In the majority of cases this decrease was accompanied by an increased basal metabolic rate. In one patient an increase in carbohydrate in the diet resulted in the return to normal of the modified sugar tolerance and increased glycogen stores. Liver glycogen reserves were estimated by the phlorhizin method of Mirsky. There was less stored glycogen in the liver following methyl testosterone treatment. This was in agreement with the finding that the liver glycogen of rabbits was decreased following methyl testosterone therapy.

We wish to thank Dr. Max Gilbert of the Schering Corp., Bloomfield, N.J., for the methyl testosterone used in these studies.

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Insulin Resistance in Diabetes Mellitus

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SINCE THE BEGINNING of the insulin era, the subject of insulin resistance has become one of increasing interest. Root (1), in 1929, termed those cases insulin-resistant which required more than 100 units daily to maintain proper carbohydrate balance. He pointed out that temporary resistance to insulin, so commonly encountered for a brief period in the comatose diabetic, properly should not be included under such a designation. He estimated, on the basis of animal experiments, that a completely depancreatized man would require 200 to 300 U daily. Undisputed cases of complete insulin resistance in man would thus be those which have a daily insulin requirement above this.

There have been published a number of isolated reports of patients who have required an abnormally large amount of insulin. These have been summarized during the past year in a paper by Martin, Martin, Lyster and Strouse (2). To these may be added two cases of Marble, Fernald and Smith (3), one requiring 300 to 1750 U daily for 2 months, the other 350 to 2000 U daily for over 7 months; and the patient reported by Levi and Friedman (4) who received an average of 1621 U daily for 47 days, the maximum daily dosage being 4000 U.

No real advance in the understanding of this resistance to insulin was made until recently, when the studies of Houssay (5) and of Long (6) began to throw an entirely new light on carbohydrate metabolism. Young (7) has investigated the problem from the laboratory standpoint, and Glen and Eaton (8) and Wiener (9) from the clinical point of view.

We are reporting a case of insulin resistance in a patient with diabetes mellitus who for almost 4 months received an average daily dose of 1195 U, a maximum daily dose of 2460 U, with a total dosage of 129,470 U. Certain investigative studies have been performed in an endeavor to throw light on the mechanism of insulin resistance.

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[1] The authors acknowledge the aid of Dr. Horace Gray and the assistance of the following members of the House Staff: Drs. J. S. Brown, F. N. Hatch, W. D. Clark and Allen Mitchell.

CASE REPORT

C.A.K., S.F.H. No. 257261,[1] was a 64-year-old married male leather worker of Irish-Portuguese parentage who was first seen at the Stanford Hospital Outpatient Department on Jan. 28, 1939. The diagnosis of pulmonary tuberculosis was made. Sugar was found in the urine at this time, but the patient did not return to the clinic. On Oct. 5, 1939, he was seen again and had then lost 17 lb. (7.7 kg.) in weight. The additional diagnosis of diabetes mellitus was made at this time. He attended the clinic a few times and on Oct. 28, 1939, was admitted to the Tuberculosis Division of the San Francisco Hospital.

Family history. Father and mother died at 66 and 57 years, of unknown causes. One brother died at 17 of tuberculosis, and another brother died at 45 from 'ulcer of the liver.' *Past history.* He had had the usual childhood diseases. In 1898 he had pneumonia without sequelae and in 1934 he had acute arthritis of the ankle for 3 months.

Physical examination. This showed a rather poorly nourished white male who appeared chronically ill. The height was 5 ft. 6 in. and weight was 139 lb. (63 kg.). He had complete adentia, bilateral reduction of hearing, moderate emphysema, physical signs indicating an infiltrative process in the left upper lobe of the lung, rather faint heart sounds, poor rectal sphincter tone, a sluggish left ankle jerk, an absent right ankle jerk, and a spermatocele. Blood pressure, 170 mm. Hg, systolic, 80 diastolic.

Laboratory examination. The blood count showed a hemoglobin of 16.3 gm. (92% Sahli), a red cell count of 4.5 million, a total white cell count of 7640, with 75 per cent neutrophils. The urine was acid, lemon-colored, clear, of a specific gravity of 1.024 and free of albumin. The Benedict test for sugar was 2+. The sediment contained rarely a squamous and a white cell. The Wassermann and Kahn reactions were negative. The corrected sedimentation rate was 34 mm. in 1 hour (Wintrobe). There were many tubercle bacilli in the sputum. The trend of the blood chemistry values during the course of the patient's hospitalization is shown by the figures in table 1. The liver function tests are recorded in table 2. They did not indicate any liver damage.

Roentgen-ray examination. This showed evidence of an inflammatory process with cavitation in the left upper lobe extending into both lower lobes, and moderate pleural thickening on the left with deviation of the mediastinum toward the left.

Course. The patient remained in the hospital until his death 7 months later. He had an intermittent low-grade fever during his entire stay, and the tuberculous process gradually spread. On Jan. 25, 1940, a pneumothorax was begun on the left side. This was technically successful and was followed by weekly refills, but the course of the disease was not arrested. Because of the continued advance of the tuberculous process in the right lung, a pneumothorax was also ordered on the right. The initial right pneumothorax was given on May 16, 1940. At this time his condition was critical. He died on May 25, 1940.

TABLE 1. BLOOD CHEMISTRY

Date	Blood Sugar, mg. %	Plasma CO_2 Combining Power, vol. %	Serum Cholesterol, mg. %	Blood NaCl, mg. %	Blood Urea, mg. %
2/ 9/40	231		231		
2/12/40	408		171		
2/29/40	250			420	15
3/11/40	377	62			
4/10/40	454	63		408	
5/16/40	384	17		436	

The course of the diabetes was not remarkable during the first 3 months of his hospital stay. He was originally given a diet of C 200, P 90, F 110, and 30 U of protamine zinc insulin. On Nov. 3, 1939, 5 days after his admission to the hospital, blood sugar specimens were taken before each meal. The values were 122, 200, and 170 mg. per cent respectively, indicating a type of response characteristic of a fairly well controlled diabetic. Because of persistent mild glycosuria, the dose of insulin was raised on Dec. 2nd to 40 U of protamine zinc insulin and 10 U of amorphous (regular) insulin. The urine remained sugar-free on this regimen for over a month. After this time glycosuria began again and continued despite an increase in the insulin intake to 95 U on Jan. 27, 1940. On Feb. 5th, the diet was changed to C 500, P 90, F 110. This was done because of the increase in insulin sensitivity resulting ordinarily from a high carbohydrate diet (10), and also because of suspected hepatic involvement. On the same date the fasting blood sugar was 280 mg. per cent and the urine showed a 4+ sugar and a 1+ acetone. The insulin intake consisted of 60 U of protamine zinc insulin and 60 U of amorphous insulin.

His course hereafter was most extraordinary. The chief features are portrayed graphically in figure 1. It was recognized that the phenomenon of insulin resistance was present. The insulin dosage was increased rapidly and progressively. On February 12th, the insulin intake was 800 U and the blood sugar was 408 mg. per cent. The quantitative sugar output was 216 gm. per 24 hours and he had a 1+ acetone in the urine. Although continued daily increase of insulin did not show any immediate result, as measured by urinary sugar output, the blood-sugar level over the next 2 weeks gradually diminished to considerably lower levels. On February 23rd the total insulin dosage was 2280 U and the fasting blood sugar was 263 mg. per cent. The urine still showed 4+ sugar and 1+ acetone. The greatest daily intake of insulin during his entire hospital stay was on February 26th, when he was given 1940 U of unmodified insulin and 520 U of protamine zinc insulin, or a total of 2460 U. During the next 10 days the dosage was gradually lowered because the blood-sugar level and the sugar output in the urine decreased markedly and the acetone disappeared from the urine. At the end of this period clinical symptoms of hypoglycemia developed. On March 6th the fasting blood sugar was 55 mg. per cent. On this day he received a total insulin dosage of 1890 U and on the following day the fasting blood sugar was 52 mg. per cent. At this time it was decided to reduce the insulin dosage drastically (11). On March 10th it had reached a value of 500 U for the total daily dosage. On this day, however, the fasting blood sugar was again markedly elevated, being 377 mg. per cent. The urinary sugar output was 170 gm. per 24 hours. The acetone was 2+. This attempt to lower the insulin dosage being obviously unsuccessful, the amount was raised in 2 days to 1380 U, on which regimen he was continued to March 31st. A Congo red test for amyloid made on March 28th showed 47 per cent retention of the dye in one hour. During this period the blood-sugar values ranged from 117 to 330 mg. per cent and the average urinary sugar output fluctuated between 72 and 198 gm. per 24 hours. The urine was free of acetone. It may be noted that the output of sugar was considerable and that the blood-sugar level still averaged around 250 mg. per cent. Clinically, the patient did not feel nearly so well as he had before this. Several times during the day and night he perspired, had symptoms suggesting hypoglycemia, and was generally uncomfortable. The daily insulin dosage was therefore further decreased to 920 U (420 U of unmodified insulin and 500 U of protamine zinc insulin). This was continued until May 20th. Throughout this period the blood-sugar level was higher, the fasting values ranging from 350 to 483 mg. per cent. The urinary glucose output varied from 234 to 402 gm. per 24 hours. Acetone, and later diacetic acid, reappeared in the urine. However, the patient felt more comfortable than he had at any time during his period of insulin resistance. Because of increased formation of diacetic acid, the insulin dosage was increased from 1220 U on May 21st to 2200 U on May 24th. Fifteen hundred gm. of glucose was given during this day. The acetone and the diacetic acid disappeared from the urine, but clinical signs of diabetic coma progressed and the patient died in the evening of May 25th, 1940.

TABLE 2. LIVER FUNCTION TESTS

Retention of bromsulphalein:	½ hr., 0 1 hr., 0
Retention of galactose:[1]	1 hr., 31 mg. % 1½ hr., 18 mg. %
Synthesis of hippuric acid:[2]	4.8 gm. found in 1000 cc urine. (Normal 3–3.5 gm.)

[1] Determined through the courtesy of Dr. T. L. Althausen.
[2] Determined through the courtesy of Dr. D. K. Burnham.

Summary of pathological findings (Dr. A. J. Cox). The autopsy, performed 16 hours after death, showed bilateral pulmonary tuberculosis, with a large cavity six cm. in diameter in the upper lobe of the left lung and many small

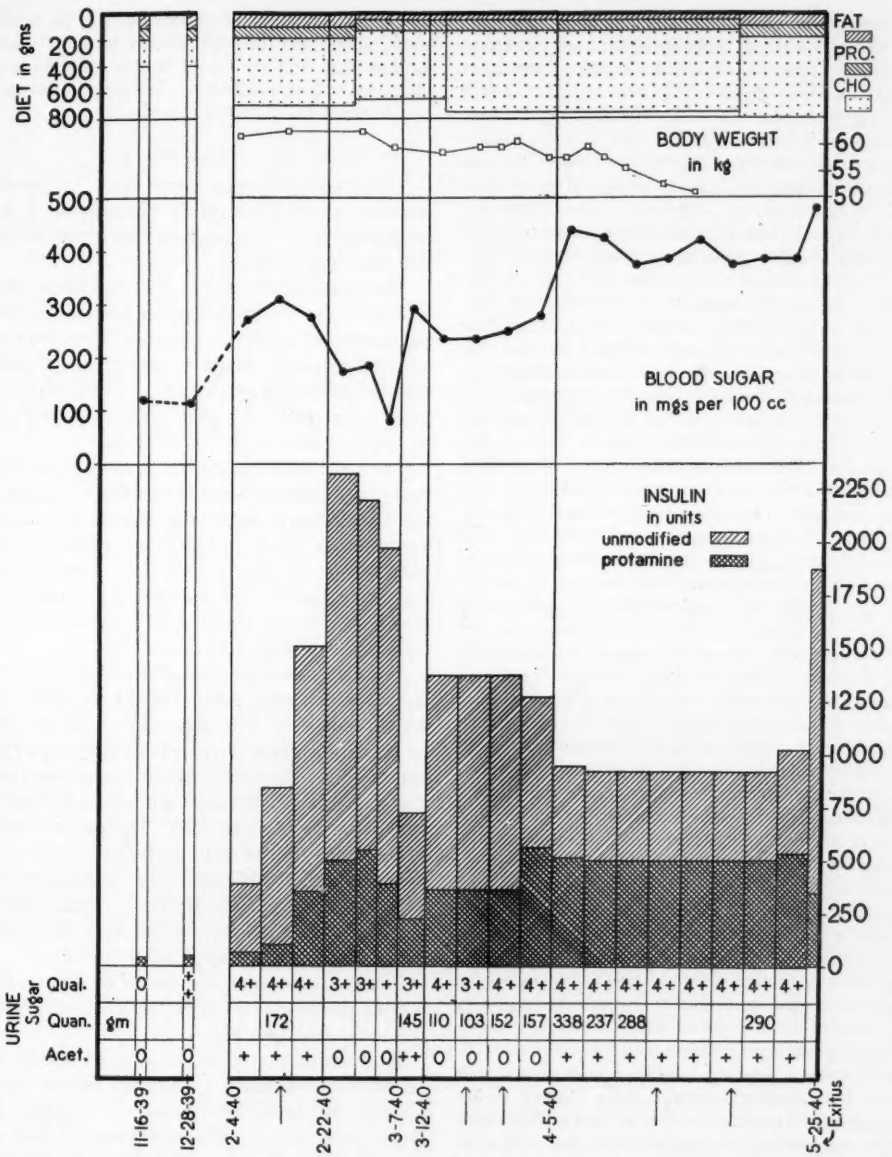

Fig. 1. DATA OBTAINED DURING PATIENT'S HOSPITALIZATION. The detached portion to the left represents the period before the development of insulin resistance. The blocks in the main body of the chart give average values for 6 days each except where rapid adjustment in the insulin dosage make this inappropriate and where corresponding adjustment in the width of the blocks is made. Each black dot on the blood sugar curve represents the average of 2 to 6 fasting blood-sugar values. The values recorded for acetonuria and glycosuria, both qualitative and quantitative, are likewise averages. The vertical arrows denote the dates on which the experiments were made.

nodules throughout the remainder of this lung as well as the upper lobe of the right lung. The right middle and lower lobes showed only an occasional small tubercle. A few tubercles were present in the moderately enlarged hilar lumph nodes, but no gross caseation was seen. Histologically, the cavity and many tubercles were surrounded by moderate amounts of fibrous tissue, indicating that they were not rapidly progressing lesions, but some of the nodules were not so demarcated.

The pancreas was 20 cm. long and its cross-section measured 1 by 3 cm. at the head. However, the body and tail were much thinner, and it was thought that the organ as a whole was distinctly smaller than normal. The markings on the cut surface were normal, as was the histo-

logical appearance of sections stained with hematoxylin-eosin, although islets of Langerhans were not numerous. The adrenals, testes, and prostate showed no significant gross or microscopic changes. The thyroid gland, although not enlarged, showed distinct evidence of hyperplasia. Its follicles varied considerably in size. In many follicles there was practically no colloid; in others the colloid was faintly stained and showed marked peripheral vacuolation. The lining epithelium was columnar in many places and many of the nuclei had unusually deeply stained chromatin. No mitotic figures could be identified with certainty. There was no lymphoid tissue in the organ. The anterior lobe of the hypophysis contained eosinophilic and basophilic cells in approximately normal numbers. A moderate number of small basophilic cells extended into the posterior lobe in one region. The remaining basophils were normal. Many contained fairly large cytoplasmic vacuoles. Many of the eosinophils were also vacuolated, but most of the vacuoles were smaller than those in the basophils and they were often multiple. In the capsule of the gland in one region were several long rows of small cells with scanty cytoplasm. The arrangement of these cells suggested that they were epithelial, but their identity could not be established. There was a slight diffuse increase in the interstitial connective tissue of the anterior lobe in places, and toward the center of the lobe was a small dense scar. However, the amount of reduction of the number of epithelial cells on this account was negligible.

The liver was enlarged, weighing 2700 gm. It was firm and pale brown. Its vessels were normal. The cut surface was uniform and slightly opaque, with no visible lobule markings. A little thick turbid blood-tinged fluid could be expressed from the cut surface. Lugol's solution stained the liver tissue deep mahogany brown, and the exuding thick fluid was similarly stained. Further tests on aqueous extracts of the liver substance showed large amounts of a substance which in solution was milky white, opalescent, and had many of the properties of glycogen. It could be precipitated by alcohol but not by heat or trichloracetic acid, and it disappeared on acid hydrolysis, yielding a substance which would reduce Benedict's solution. Although no quantitative determinations were made, the substance remained in apparently undiminished quantity in specimens of the liver stored in the ice box for 2 weeks. Similarly, incubation of pieces of liver for 4 days at 37° C. did not destroy it, whereas incubation with ground liver obtained from another autopsied body resulted in disappearance of the substance within 24 hours. Histological study showed marked enlargement of the liver cells, some of which had nearly twice the normal diameter. Most of the sinusoids were collapsed. The nuclei of the large cells were normal but the cytoplasm was practically unstained except for a thin rim at the cell margins. Best's carmine stain showed abundant masses of glycogen in these cells. No amyloid was present. No glycogen was demonstrable in any other organs.

The spleen weighed 240 gm. Its pulp was firm and dark red. The heart weighed 230 gm. and appeared normal. No glycogen could be demonstrated in the muscle either by gross iodine test or by using Best's carmine stain on alcohol-fixed tissue, although many of the muscle fibers contained fine vacuoles. There was relatively little arteriosclerosis, the most marked lesions being in the descending aorta, where, near the bifurcation, were several scattered medium-sized slightly raised intimal plaques without ulceration or gross calcification. The kidneys were normal. No abnormalities were found in the brain.

COMMENT

This case represents an example of insulin resistance which began fairly abruptly in a patient whose diabetes had been quite well controlled during the preceding 3 months.

The course of the patient after he became resistant to insulin may be divided into 5 periods according to the amount of insulin he received. The lines running vertically through figure 1 mark these off abruptly into the following periods: *a*), rapidly increasing insulin requirement; *b*), peak dosage; *c*), low dosage; *d*), higher plateau; *e*), lower plateau.

The most striking feature of the case is the fact, best gleaned from the composite chart, that the average fasting blood sugar, the glycosuria and the ketonuria were almost inversely proportional to the insulin dosage. In other words, the response to insulin was much like that of the ordinary diabetic except that huge doses of insulin were necessary to produce a glucose-lowering effect in the blood.

The case was studied carefully to rule out various factors which have been thought to play a rôle in insulin resistance. The effect of diet did not seem to be important. Shortly after the beginning of the resistant stage, the carbohydrate intake was raised to 500 gm. a day. Thereafter the scheduled diet contained 500 to 600 gm. daily. The patient often left some of this on the tray, probably enough to affect the individual blood sugar values but not enough to affect the averages. The fat intake varied from 40 to 100 gm. a day. It was thought that the higher fat intake was associated with greater ketonuria.

There was no clinical evidence of allergy. In comparison to the amount of protein-containing solution, the tissue reactions were slight.

Since sources of insulin may have a bearing on the problem of insensitivity several brands were employed, including amorphous or 'regular' insulin (beef, pork and sheep)[2] and solution of zinc insulin crystals and protamine zinc insulin.[3] No difference in effect was noted.

INVESTIGATIVE STUDIES

Houssay (5) has shown that injections of the anterior lobe of the pituitary gland into dogs produces a temporary diabetic state. More recent work by Jensen (12), Young (13), and others has suggested

[2] The various brands of regular insulin used were manufactured by Eli Lilly Co., Indianapolis, Ind., Sharpe and Dohme Co., Philadelphia, Pa., and Frederick Stearns & Co., Detroit, Mich.

[3] The solution of zinc insulin crystals and the protamine zinc insulin used were manufactured by Eli Lilly Co., Indianapolis, Ind.

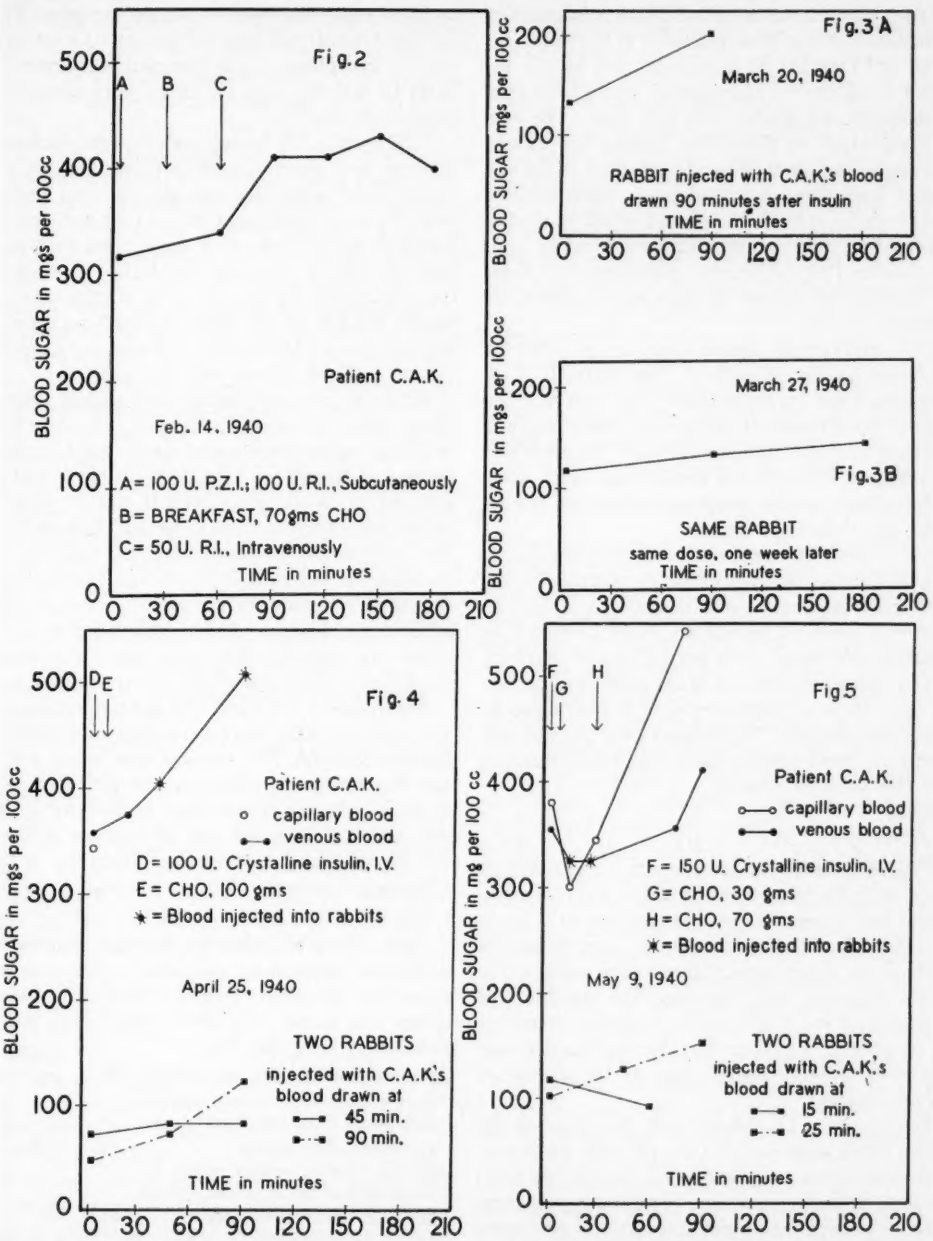

Fig. 2. INSULIN-CARBOHYDRATE TOLERANCE test illustrating continued rise of blood sugar despite repeated large doses of insulin.

Fig. 3. RISE IN BLOOD SUGAR of a rabbit after injection of blood from the patient despite previous injection of 120 U of amorphous insulin subcutaneously into patient.

Fig. 4. UPPER FIGURE is an insulin-carbohydrate tolerance curve illustrating the continued rise of the blood sugar of the patient despite a large dosage of insulin intravenously. The lower figure shows the lack of an insulin effect and the presence of a hyperglycemic effect in the patient's blood as determined by its injection into rabbits. The rabbits' blood sugar rises rather than falls.

Fig. 5. UPPER FIGURE shows two insulin-carbohydrate tolerance curves, illustrating the continued rise of the patient's blood sugar after an initial drop caused by a very large dose of insulin intravenously, and the differences in the values of the sugar in the capillary and the venous blood. The lower figure shows the insulin-effect present in the patient's blood as demonstrated by the rabbit method when blood is withdrawn 15 minutes after insulin injection and the hyperglycemic effect when blood is taken at 25 minutes.

that the ability to utilize carbohydrate is inherent in the tissues and that this utilization is facilitated by insulin and retarded by factors secreted by the anterior lobe of the pituitary gland. Young separated the pituitary 'antagonist' into two parts. The first of these, which he called the 'glycotropic' factor, antagonized the action of insulin although it did not produce hyperglycemia or diabetes when injected into the normal animal. The second, which he termed 'diabetogenic,' also antagonized insulin but in addition produced hyperglycemia, glycosuria, and ketosis. Continuation of its injection led to permanent diabetes.

In the study of this patient during the period of his manifested insulin insensitivity, two methods of investigative procedure were used. The first was the study of the response of the patient's blood sugar to subcutaneous and intravenous insulin; the other was the response of a rabbit's blood sugar after intraperitoneal injection of blood specimens from the patient under these circumstances.

Experiment 1[4] (*fig. 2*). On Feb. 14, 1940, the fasting blood sugar was 316 mg. per cent. At this time he was given 100 U of amorphous insulin and 100 U of protamine zinc insulin. One-half hour later he ate a light breakfast containing about 70 gm. of carbohydrate. After another half-hour the blood sugar was 341 mg. per cent. He was then given 50 U of amorphous insulin, intravenously. The values of the glucose content of the blood samples taken at half-hour intervals after this were as follows:

Hours	.5	1	1.5	2
Mg. per cent	411	411	429	400

This experiment demonstrates that there was no lowering of the blood sugar by either 100 U of amorphous insulin given subcutaneously or 50 U given intravenously. The rise of the blood sugar proceeded much as one might expect after a meal without the benefit of insulin administration. The possibility of an immediate and transient fall cannot be denied but the occurrence of a progressive rise after such a large dose of intravenous insulin suggests the absence of any insulin effect.

Experiment 2. On March 20th the value of the fasting blood sugar was 117 mg. per cent for the venous blood and 113 mg. per cent for the capillary blood obtained by finger puncture. The patient was given 120 U of amorphous insulin and 120 U of protamine zinc insulin, subcutaneously. One and one-half hours later 10 cc. of venous blood were withdrawn and injected immediately into the peritoneal cavity of a 2-kg. rabbit kept in a fasting condition. The rabbit's fasting blood sugar just before the injection was 133 mg. per cent (fig. 3, *a*). One and one-half hours later its blood sugar had risen to 210 mg. per cent. Thus the blood transferred from the patient 1.5 hours after 120 U of amorphous insulin conveyed to the rabbit no factor for utilizing sugar but actually the blood had a hyperglycemic effect.

Experiment 3. On March 27th the experiment was repeated in a slightly modified form. The patient's fasting blood sugar was 246 mg. per cent and the rabbit's fasting blood sugar was 117 mg. per cent. An intraperitoneal transfer of 10 cc. of blood withdrawn from the patient 1.5 hours after he had received 120 U of amorphous insulin and 120 U of protamine zinc insulin yielded, in the rabbit, a blood sugar of 132 mg. per cent 1.5 hours after injection, and a value of 142 mg. per cent 3 hours later (fig. 3, *b*).

Although the curve changes only slightly from the initial value, the important fact is that it rises instead of falling. Such a rise has been said to occur in rabbits anyway (although we have been unable to find any such report in the literature). If this be true, the phenomenon remains remarkable until it is explained. The explanation we postulate is the existence of a diabetogenic factor. It is of interest that the rise in the rabbit's blood sugar was greater in *experiment 2*, at the time of which the patient's blood sugar was lower (*i.e.*, insulin effect was more pronounced). Confirmation of this is offered in *experiment 4* and *5*.

Experiment 4. On April 25th the patient was given 100 U of crystalline insulin intravenously while in a fasting condition. Five minutes later he ate a breakfast containing approximately 100 gm. of carbohydrate. Blood samples were then withdrawn at intervals measured from the time of injection of insulin. The blood sugar values were as follows (fig. 4, top):

Minutes	0	20	45	90
Mg. per cent	356	375	405	515

When blood was taken for chemical analysis at 45 and at 90 minutes, an additional 10 cc. was withdrawn for immediate injection into the peritoneal cavity of a rabbit. The blood sugar values were as follows (see fig. 4, bottom):

Minutes after injection into rabbit	F	45	90
Mg. per cent first rabbit, injected with 10 cc. of patient's blood drawn 45 minutes after insulin	121	128	129
Mg. per cent in second rabbit, injected with 10 cc. of patient's blood drawn 90 minutes after insulin	97	121	173

Incidentally, the patient's initial capillary blood sugar was 346 mg. per cent when his venous blood sugar was 356 mg. per cent; the difference may merely be within the accuracy of the chemical technique; nevertheless, this is commented upon because the arterial is lower than the venous value, instead of higher, as is usually expected. This phenomenon also occurred in *experiment 2*. Griffiths (14) found that in

[4] Dr. W. C. Cutting aided in the preparation of these experiments.

young and old diabetics alike the arteriovenous blood sugar difference was smaller than in the normal individual. He called attention to the frequent occurrence of negative arteriovenous differences in the diabetic and its rarity in the normal individual but could offer no explanation. The rabbit experiments demonstrate that, 45 to 90 minutes after a large intravenous dose of insulin, this patient's blood, when transferred to rabbits, not only failed to lower the rabbit's blood sugar, but, on the contrary, caused it to rise. We see in this a hyperglycemic factor. This substance may have developed before the collection of the 45-minute specimen, but sufficient quantity for demonstration was found only after a longer interval. On the other hand an 'anti-insulin' or 'glycotropic' effect was already present at 45 minutes. This suggests the possibility of the separate identity of the anti-insulin and hyperglycemic factors.

Experiment 5. On May 9th the last experiment was repeated, with certain changes. First, the comparative capillary and venous blood-sugar values of the patient were studied over a longer period, *i.e.*, 1.5 hours after 150 U of crystalline insulin had been injected intravenously (fig. 5, top); second, the effect of the injection of 10 cc. of venous blood into rabbits was observed when drawn at shorter intervals, *i.e.*, 15 and 25 minutes after the insulin injection into the patient (fig. 5, bottom).

The blood sugar curves obtained were as follows:

Time in minutes		F	15	25	70	80	90
Blood sugar in mg. per cent	Venous	405	375	374	405		455
	Capillary	430	350	396		545	

The blood sugar values of the rabbits were as follows:

Minutes after injection into rabbit	F	45	60	90
Mg. per cent in first rabbit, injected with 10 cc. of patient's blood drawn 15 minutes after insulin	117		87	
Mg. per cent in second rabbit, injected with 10 cc. of patient's blood drawn 25 minutes after insulin	101	132		151

The findings of this experiment further support the conclusions reached in the preceding experiments. Again there was an absence of the expected positive arteriovenous difference occurring after the ingestion of food and a dose of insulin (fig. 5, drop in open circle lines).

This time the intravenous administration of a large dose of insulin given in conjunction with only a small carbohydrate meal (fig. 5, *G*) did produce a depression of the blood-sugar level which lasted for about 70 minutes.

The rabbit experiments can best be interpreted to signify that 15 minutes after the intravenous administration of a large dose of insulin into the patient (fig. 5, *F*), enough active insulin was contained in it to lower the blood sugar of the rabbit. This was the sole instance in our experiments in which the transfer produced the anticipated sugar-utilizing effect. Ten minutes later (fig. 5, second asterisk), with the level of the patient's blood sugar quite unchanged, no demonstrable insulin effect on the second rabbit could be shown (fig. 5, dash-dot line). In addition, this finding lends further support to the contention that the glycotropic factor present in this patient's blood was a substance completely separate from insulin. One may speculate whether this factor was present, temporarily depressed in its action by large amounts of insulin, or whether it was the result of a hypothetical insulin inactivator or antagonist in the patient.

DISCUSSION

The investigative studies on this patient were originally undertaken in an effort to study the effect of insulin on the blood sugar of the patient and to demonstrate the presence of insulin in the blood of the patient after injection. It has been stated (15) that 2 to 4 U of insulin will produce shock in a rabbit and that about one-third of a U is necessary to produce a certain blood-sugar lowering effect. If one were to assume the patient's blood volume to be 6000 cc., it would appear that in the rabbit experiments there should have been one-fifth U or more in each sample removed for animal inoculation, were the insulin still present in an active form 15 to 90 minutes after its injection into the patient. However, if one grants that within a few minutes insulin diffuses throughout the interstitial fluid, the dilution factor should be in the neighborhood of 18 liters; this would mean that about 1/15 of a unit would be contained in each transfer. This amount seems hardly sufficient to produce any lowering of the blood sugar of the rabbits, and in fact, in only one instance did any such depression occur. On the contrary, the blood-sugar values were usually higher. In general, the rise appeared to become more marked as the time interval after the injection of insulin into the patient increased. These results offer confirmation of Glen and Eaton's findings (8) that the injection of the serum of their insulin-resistant patient into rabbits induced an active insulin antagonism in them and that this was more marked if the patient had had insulin one-half hour before withdrawing the blood.

De Wesselow and Griffiths (16) injected the plasma of certain elderly diabetics into rabbits and found that the duration of the hypoglycemia produced by intravenous insulin was reduced whereas the blood of young diabetics had no such effect. This suggested

to them the presence of a pituitary-like diabetogenic factor rather than lack of insulin. They considered the older individuals to be insulin-resistant in type and the younger ones insulin-sensitive. Marble, Fernald and Smith (3) were unable to obtain such an insulin-inhibiting substance from the plasma of 30 diabetic patients, chiefly elderly, except from the blood of their two insulin-resistant subjects. Griffiths (14) performed insulin-glucose tolerance tests on both types of diabetics and on normal individuals. The control subjects and the young diabetics showed a response to insulin while the elderly ones did not, that is, their blood sugar continued to rise over the period of the test (which was 1.5 hours). The blood-sugar response of our patient was similar to that obtained in these so-called insulin-resistant patients, within the limits of the changes in technique of the test. The amounts of insulin used by us were, of course, very much larger.

Griffiths (14) concludes that resistance was 'mainly due to the inability of the hormone to exert to the full its control over the storage of sugar in the liver.' Wilder (17), too, believes that the liver is principally at fault in many cases of marked insulin insensitivity. The large amount of glycogen in the liver found at autopsy in our case indicates a defect in the glycogenolytic process. Whether this may have been due to the presence of a specific substance in the liver (18) or to the direct effect of the insulin-antagonist remains a matter of speculation.

The substance found by Glen and Eaton (8) in their case of insulin resistance and the factor found in our patient are probably the same. In both, evidence was found of a factor antagonizing the action of insulin, although the methods used for its demonstration were different. In our case a hyperglycemic factor has also been demonstrated. Whether or not this is identical with the insulin antagonist or whether it represents a separate fraction, we cannot say. The work of Houssay (5), Young (7), and others previously cited has demonstrated that the anterior lobe of the pituitary gland may produce effects similar to those produced in these studies. The pathological evidence of overactivity of the thyroid gland, suggesting activity of the thyrotropic hormone of the anterior lobe of the pituitary adds further support to the hypothesis that this gland is responsible for the anti-insulin and hyperglycemic effects which have been demonstrated.

SUMMARY AND CONCLUSIONS

1. A case of complete resistance to insulin is reported. This patient was given from 500 to 2460 U of insulin daily for a period of almost 4 months.

2. A search of the literature has revealed 20 cases of marked insulin resistance in diabetes mellitus.

3. Experimental observations indicated that although this patient was highly resistant to insulin, he nevertheless utilized insulin to some degree.

4. Insulin-carbohydrate tolerance tests made with samples of blood taken at one-half-hour intervals demonstrated very little effect on the blood sugar despite very large doses of insulin given subcutaneously or intravenously. A definite depression of the blood-sugar level was obtained when the intravenous dose of insulin was large enough (150 U).

5. Insulin was demonstrated in the blood stream of the patient after its administration to him. Enough insulin to depress the blood sugar of a rabbit was present 15 minutes after the injection into the patient of insulin intravenously in one experiment, but this effect had disappeared after 25 minutes.

6. A substance capable of elevating the blood-sugar levels of the rabbits was repeatedly demonstrated in the patient's blood. This hyperglycemic effect became more pronounced as the immediate effect of the insulin wore off.

7. The data suggest that the phenomenon of insulin resistance, in this patient at least, was produced by the presence of an insulin antagonist. Whether this was identical with the hyperglycemic factor or whether it represented a separate fraction, we cannot say.

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Combined Use of Testosterone Propionate and Psychotherapy in Treatment of Hypogonadal Behavior-Problem Boys

[Treatment of Hypogonadism]

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THE CLOSE relationship between the endocrine system and neuropsychiatric functions is becoming more and more recognized. The evidence pointing to this interrelation has been accumulating from many sources. Thus, anatomical (1), biochemical (2), psychological (3), neuropathological (4) and clinical studies (5–7) have all played a part. The observation by Rowe (8) that approximately 75 per cent of 374 problem children disclosed definite evidence of pituitary defect represents one of the most exhaustive clinical studies bearing upon the problem.

The frequent occurrence of endocrinopathy and misbehavior in children may indicate that a common genetic factor is responsible for both the physical and mental aberrations. Personal observation, however, has led to the impression that the problem behavior of many endocrinopathic children like the misbehavior of the normally constituted child is frequently experientially-determined. Such a child, because of his somatic disfigurement becomes the target of jibings and excoriating epithets inflicted by other children and even by childishly humored adults. Reactions of depression or compensatory aggressions soon follow.

While psychotherapy is undoubtedly helpful for the adjustment of such patients it naturally fails in itself to alter the bodily defects which initiated the series of experiences responsible for the reactions. The proper use of endocrine preparations, therefore, becomes important. This is particularly true in genitally hypoplastic boys since the synthetically prepared male sex hormone, testosterone propionate, has now become available in sufficiently pure form and in sufficient quantities for clinical use.

The following case reports will disclose the problems encountered and the results obtained in a series of such hypogonadal problem children.

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CASE REPORTS

Case 1, S.K., a white male 12 years and 9 months of age presented a typical dystrophia-adiposo-genital syndrome with characteristic shoulder-pelvic-girdle adiposity and infantile genitalia. The penis was 2 cm. in length. The parents complained of the child's misbehavior in school. He frequently interrupted the teacher's remarks in order to correct what he considered to be erroneous statements and he insisted on calling out the answers to questions directed to other children.

He was mentally alert, very boastful and spoke of his intellectual superiority over other children. He never cried about his genital abnormality nor was he overemotional in other respects. But he refused to undress in the gymnasium and to enter in the nude the swimming pool at school. On the Binet-Simon test he displayed a mental age of 18 years 3 months and an intelligence quotient of 143.

Here we were dealing with a mentally precocious child with dysplastic constitution whose judgment, still in keeping with his chronological age, permitted him to flaunt his mental superiority before his class-mates. As a result he became the shunned member of his class. Left to himself he became more egocentric and self-sufficient.

He was treated with anterior pituitary extract[1] twice weekly, and placed on dietary restriction. Although he lost weight with this treatment, at the end of 2 months the genitals had failed to develop. He was, therefore, given additional subcutaneous injections of testosterone propionate twice weekly in doses of 25 mg. for the first month, 10 mg. twice weekly during the 2nd month and 5 mg. (each injection) thereafter. Psychotherapy by way of persuasion and re-education in order to improve his personality traits and social relations was also included. Only after 9 months of such treatment when the bodily form approached the normal and the penis had grown to a length of 5 cm. with a circumference of 6 cm. did he make a satisfactory adjustment toward his work and playfellows. He then saw and accepted his previous forwardness and conceit in school as an overcompensation for his feelings of inferiority to other children.

[1] The anterior pituitary extract was supplied by E. R. Squibb and Sons, New Brunswick, New Jersey.

Case 2, M.S., a white male 14 years of age also presented the syndrome of dystrophia-adiposo-genitalis. The penis was 2 cm. in length and 4 cm. in circumference. In addition, the testes were bilaterally undescended. These, however, could be palpated in the inguinal canals. Unlike the previous patient, he was slow in action, shy and retiring, and refrained from all games with other boys. His mental age (Binet-Simon) was 12 years; the intelligence quotient was 86 and the B.M.R. −15. Thyroid 1 grain, twice a day soon raised the B.M.R. to −8. Testosterone propionate,[2] 10 mg. twice weekly, injected subcutaneously over a period of 3 months resulted in more normal bodily configuration, a penile development to 5 cm. in length and 6 cm. in circumference with bilateral descent of the testes. In addition, he became more alert mentally and advanced on the Binet-Simon scale to an I.Q. of 98 (mental age 14 yr., 1 month). His attitude toward other children improved so that he spontaneously engaged in combative sports with the boys of the neighborhood.

Case 3, D.B., an 11-year-old white male was seen in June, 1938, because of disrespect, moodiness, temper tantrums and frequent fights with other children. These complaints dated back about 2 years, prior to which time he had been quiet and had seemed almost too well behaved. He made very good marks in school but here, too, he had become talkative and boastful. The patient spent a good deal of time with his mother and as an only child had been pampered. The first indication of behavioral change had occurred when the mother, as was her usual custom, attempted to bathe him. He refused to expose himself before her and in response to her insistence gave way to an outburst of temper which for him was something new. This was followed by a crying spell.

Physical examination disclosed a normal height (56.7 in.) but a weight of 110 lb. which was about 31 lb. above the maximum normal of 79.4 lb. (9). There was no skeletal disproportion. The fat deposition was of the shoulder-pelvic-girdle type. The breasts were also obese but disclosed no evidence of mammary tissue. The genitalia were diminutive. The left testis had descended but the right testis was still in the inguinal canal and could not be pushed into the scrotum. Each testis was about the size of a small filbert nut. The penis was infantile in appearance being only 1.5 cm. in length. Neurological findings were essentially normal but the right cremasteric reflex was absent. B.M.R. was −19. The results of other laboratory studies were normal. Mentally the child was alert, spoke relevantly, was well behaved and co-operative. He could not explain why he mishaved and when asked if it might be because he wanted something which he did not possess he replied that he had everything and even boasted of his superiority over other boys. Binet-Simon test revealed a mental age of 12 years 7 months and an I.Q. of 114.

Treatment consisted of a diet containing 1533 calories, an amount which was based on a body weight of 70 lb. It consisted of protein 65 gm., carbohydrate 127 gm. and fat 85 gm.; thyroid, .5 grain 3 times a day adequate vitamin intake; testosterone propionate, 5 mg. twice weekly by subcutaneous injection. In addition, psychotherapeutic discussions elicited that he was painfully aware of his genital inferiority, having made comparisons with other boys. His aggressiveness was merely to show these other boys that he could still be their superior. His recent recognition of his own difference from other boys was responsible for his sudden reluctance at disrobing before his mother. His temper outburst was his substitute for a more active form of aggression. By the end of November, 1938, after 5 months of treatment he showed an excellent physical change. The penis had grown to 3 cm., the height had become 58.3 inches (a growth of 1.6 in.) and the weight was reduced to 102 lb. (a reduction of 8 lb.). The most striking result however was observed in his behavior. He again became the 'good boy' at home although he remained adamant in his refusal to permit bathing by his mother. The fighting had stopped but wrestling became his favorite sport. Treatment was discontinued. Three months later his behavior was still satisfactory. Figure 1 shows a comparison of the genitals before treatment and 3 months after cessation of treatment.

Case 4, H.S., a white male 14 years and 1 month of age, was referred in November, 1938, because he 'acted peculiarly' at home. This peculiar behavior dated from the death of his father 2 years previously. At that time he went to live in the home of an older boy cousin who discovered that the patient had small genitals and taunted him about it. This so shamed him that he avoided other children whenever he could. He had frequent periods of sadness which were brought on either by thoughts of his deceased father or if he argued with his uncle with whom he lived. He felt that the uncle was taking advantage of him and his mother. Because he was now aware of his own defects, he felt that he would never be able to do anything about his uncle's unfairness, especially since he felt that he would always remain 'weak and boyish.' The difficulty concerning the uncle was found to have arisen from the patient's impression that the business affairs of his mother were being mishandled by the uncle. The mother, however, did not corroborate this accusation. At home the patient always wished to remain alone, although by his own admission he liked to listen in on the conversation of others from an adjoining room where he was supposedly studying.

Physically he was of normal height, 59.3 inches (normal range, 58.6–62.8 in.) and weighed 110 lb. (normal range 81.1–102.9 lb.). His lower bodily measurement of 30.8 in. was 2.3 in. longer than his upper measurement of 28.5 in. Normally, this difference should have been about 1 in. He disclosed a moderate obesity of the shoulder-pelvic-girdle type, a penis 1.5 cm. in length, very small testes which, however, were well descended in the scrotum. The findings in a neurological examination were normal. Psychiatric survey disclosed a shut-in type of personality with marked feelings of resentment against his cousin for teasing him and against his uncle whom he considered a cheat. The results of all of the laboratory studies made were normal. Binet-Simon test disclosed a mental age of 16 yr. and an I.Q. of 113.

[2] The author acknowledges with appreciation the aid of the Ciba Pharmaceutical Products Company Inc. for supplying the testosterone propionate (Perandren) and for partially defraying the expense of these studies.

Treatment consisted of subcutaneous injections of testosterone propionate 3 times weekly. This was given consecutively in doses of 5 mg. for 3 injections, 10 mg. for 5 injections, 25 mg. for 7 injections, 10 mg. for 5 injections, and 5 mg. each for the remaining 10 injections. During these 10 weeks the patient was also treated psychotherapeutically. He could reason very well so that he could readily be made to see the inadequate basis for his suspicion of his uncle. He soon stated that he had placed his uncle in the same category as the uncle's son, *i.e.*, the cousin who had made him so painfully aware of genital inferiority. As the phallus developed it was easy for him to accept the jibings of his cousin as manifestations of a childish sense of humor. By this time the height had become 60.2 inches (an increase of 0.9) and the weight was reduced to 105 lb. (loss of 5 lb.). The penis had grown to 6.5 cm. in length and 8 cm. in circumference. A crines pubis made its appearance. Treatment was discontinued. Three months later a communication from his mother disclosed that 'his behavior has changed more than I can tell you. He used to be moody and very distant. It would take him a very long while to make friends. He has become more forward and acts more as if he were on the same footing with others. He was always kind but now he seems more than ever to take up for the underdog.' Figure 2 shows the genital changes in this patient.

Case 5, P.S., a white male, 11 years and 10 months of age was referred in March, 1941, because of peculiar motions of his mouth, vicious temper, stinginess and rudeness. The boy's father had deserted the mother 3.5 years previously. About 1.5 years ago the child learned of his mother's intention to remarry. Soon thereafter he began displaying various tics. At the time of his first visit, he twitched his mouth and evoked a peculiar expiratory grunt. He cried easily and bragged a good bit about his cleverness, particularly regarding matters of money. He refused to spend his own money and spoke of its great accumulation as the goal toward which to strive. He took a delight in teasing his mother and frequently made remarks in the presence of her second husband threatening to tell him of some secret about her. The mother had found it very difficult to discipline the child since he took advantage of their congested living quarters and cried so loudly at the least provocation that the landlord who lived just below them threatened to make them move. The mother would then yield to his demands.

Examination disclosed a well grown boy whose height of 59.7 in. was 0.9 in. taller than the maximal normal of 58.8 in. for his age. The weight was 115.8 lb. about 17 lb. above the maximum normal of 99 lb. for the height. The skeleton showed a eunuchoid disproportion, the upper measurement being 28.1 in. as compared to a lower measurement of 31.6 in. The genitalia were extremely small. The penis was 1 cm. in length, the right testis was palpable in the diminutive scrotum but it was also tiny. The left testis could not be felt in the scrotum or inguinal canal. Neurological examination merely disclosed numerous repeated, stereotyped and imitable twitching movements of the lips with occasional expiratory grunting. These could be controlled by persuasion. No evidence of organic neurological defect was noted. Mental survey disclosed a personality of selfish, bullying, argumentative make-up. While cowardly in the presence of other boys, he was disrespectful and threatening when alone with his mother. He complained that other boys did not like him and when asked why he replied 'Because I'm different.' When asked to explain further he placed the difference on the basis of religion. The mental age was 13 yr. and 4 months and the I.Q. was 112. Basal metabolic rate was −17. The results of all other laboratory studies made were normal. Only once did he allude to a feeling of having been cheated. By this he meant his father's desertion and his sense of being different from others. He would not elaborate on the latter, but because he would never undress before other boys it was assumed that his awareness of a difference had a basis in other than mere religion.

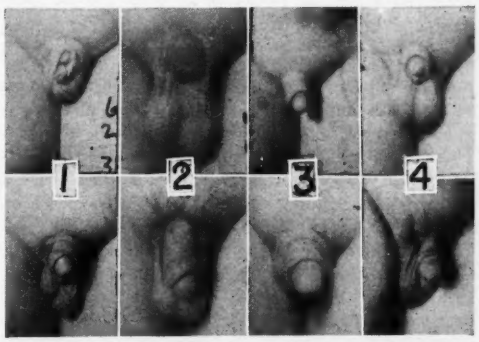

Fig. 1. *Case 3, D.B.*, 11 YEARS OLD; *upper*, June 1938; *lower*, Feb. 1939, 3 months after cessation of testosterone propionate therapy for 5 months.

Fig. 2. *Case 4, H.S.*, 14 YEARS OLD; *upper*, Nov. 1938; *lower*, Feb. 1939, after 10 weeks of therapy with testosterone propionate.

Fig. 3. *Case 7, N.M.*, 11 YEARS OLD; *upper*, Dec. 1938; *lower*, March 1939, after 10 weeks of therapy with testosterone propionate.

Fig. 4. *Case 8, D.L.*, 14 YEARS OLD; *upper*, Dec. 1938; *lower*, March 1939, after 3 months of treatment with testosterone propionate.

Here we were dealing with a boy whose obvious resentment toward his mother's remarriage was manifested by temper tantrums, growing disrespect, and threats to expose her as an attempt to embarrass her. Therapeutically however, not only did the boy require attention but the home situation called for radical revision. Accordingly, treatment was directed toward discussion with the parents concerning the establishment of a more uniform attitude. The mother was urged to consider her son just another human being and to be guided in her response to his insults as she would to a stranger's. For example, when asked what she would do if a strange child spoke to her as her own child did, she immediately responded that she would 'cut him cold.' That same attitude of aloofness until the child spoke to her with the respect which he had previously displayed was therefore decided upon. It is interesting that the patient and step-father got along well together, perhaps because the latter did little to discipline the boy.

His allowance thereafter was to be earned on the basis of proper execution of assigned tasks rather than to be received as an expected and outright donation. Discussion was carried on with the patient in order to build up a feeling of security and appreciation. Past grievances which he held against his mother were discussed and dispelled. At the same time subcutaneous injections of testosterone propionate were given twice weekly in 25 mg. doses for the first 12 treatments. For the next 9 weeks the dosage was decreased to 5 mg. each. By that time the genitals had shown excellent growth and both testes became lodged in the scrotum. But most important, his behavior had improved. He was therefore discharged. When seen 2 months later there were no complaints from either parent or child. He had become more obedient, was more respectful, said he felt 'more like a man,' and had developed a genuine feeling of security. He no longer considered himself as having been cheated. The tics had disappeared.

Case 6, R.M., white male 16 years of age, was seen because, according to his mother, he was thin, very shy, had a squeaky voice and seemed otherwise to be effeminate. These complaints dated from about 2 years previously. Prior to that time he had been apparently normal. He was a good student, in the last year of high schoool. He had always been interested in boys' activities and had been fond of hiking. Recently, however, he avoided more and more the swimming and gymnasium classes in school. As a matter of fact he, very early in the interview, asked if a note would not be written to the gymnasium instructor requesting that he be relieved from this course. At first he gave as an excuse for this request that he felt weak. Somewhat later he mentioned his self-consciousness and feelings of inferiority because of his being different from other children.

Physical examination disclosed a lad of normal stature (62.3 *in.*) who weighed but 83 lb. (minimum normal for his age was 91.6 lb.). The skeleton was disproportionate, being 28.5 and 33.7 in. for the upper and lower measurements, respectively. The skin was sallow and the face was hairless. The genitals were rather small, the penis being 6 cm. in length and 4 cm. in circumference. The testes were about the size of pigeon eggs but were well descended into the scrotum. A slight crines of the feminine type was present. Findings in the neurological examination were normal. Mental survey disclosed a marked dependence upon his mother with a desire for attention so frequently seen in early childhood. The B.M.R. was −27. All other laboratory findings were normal. On the Binet-Simon test he showed a mental age of 17 yr and 4.5 months and an I.Q. of 111.

The treatment consisted of injections twice weekly of testosterone propionate, 25 mg., for 16 weeks By this time the penis had grown to 8 cm. in length, the crines had become masculine in type, and the voice had become deeper. He now was more talkative and once again was active in hiking parties; he lost his shyness and re-entered the gymnasium class. At home his attitude toward his mother and sister became more sympathetic and more like that of a mature person. In contrast to previous behavior he no longer permitted himself to be babied at home.

Case 7, N.M., white male child, 11 years of age, failed to get along with other children because he always wanted to be the boss or the chief. He made good marks in school but there, too, had no intimate classmates. He therefore spent most of his free time alone. He would then be observed to bite his nails and occasionally cry. The family physician was consulted and on examination he discovered the child's hypogenitalism. Believing the boy's misbehavior to be related to the small genitalia he referred the patient for aid in adjustment.

Examination disclosed a quiet well behaved child of 54.5 in. in height which was normal for his age. The weight was 84.5 lb., somewhat heavier than normal. The moderate obesity was distributed over the shoulder and pelvic girdles, breasts, abdomen, upper thighs and mons pubis. There was also a noticeable degree of genu valgum. The genitalia were infantile in appearance. The penis was 3 cm. in length and extremely narrow in width. The scrotum was shallow and contained a very small testis on the left side. The right testis was absent from the scrotum and could not be felt in the inguinal canal. Several days later, this testis appeared in the upper inguinal canal only to disappear again the next day. There were no neurological defects. The findings in all laboratory tests made were normal. Psychiatric survey showed no striking evidence of affective or content disorder. He did feel, however, that he ought to be the leader in games because he felt he could not let the other boys tell him what to do. At no time did he allude to his hypogenitalism, and no discussion was held at this time concerning this deficiency. Binet-Simon disclosed a mental age of 10 yr. and 10 months and the I.Q. was 98.

Treatment consisted in discussions concerning the fairness of taking turns in leadership with other children, the importance of team work for success, and a definite schedule for play with other children was prescribed. This included classes at the local gymnasium in an attempt to develop an attitude of acceptance toward the group.

Injections of testosterone propionate, 10 mg., were given three times a week for 2 weeks. At the end of this time both testes were in the scrotum and remained there. Dosage was then dimininished to 5 mg., three times weekly for 2 weeks and was then further decreased to 5 mg. twice weekly for the next 8 weeks. The penis by this time was well grown, reaching a length of 6 cm. The scrotum, too, was well developed (fig. 3). As a matter of fact the whole body took on a more normal configuration. A small crines began to make its appearance. After the first month of treatment he began making a good adjustment towards his school-mates and in the gymnasium. His spirits improved. His previous attitude of belligerence toward the other boys was then brought up for discussion and it was disclosed that he had been made aware of his hypogenitalism several years earlier in a 'test' held by some older boys. From that time on he had frequently brooded over the defect but had never spoken of it to anyone.

Case 8, D.L., was referred when he was 14 years and 3 months old because he had become obstinate and bashful. He had begun to gain excessive weight at 9 years of age but had apparently gotten along well with other children and at home until 1.5 years before his visit. At that time

he began associating with older boys. In contrasting his own appearance with theirs he had noticed the small size of his genitals. He then made similar comparisons with boys of his own age and observed that he 'was also smaller than they.' Evidently the other boys were making their own observations, since they began to tease him and called him 'pee-wee.' Thereafter he refrained from participating in their games, remained more to himself and became bashful. The stubbornness was brought out when his mother, observing his tendency to remain at home after school, insisted upon his going out to play. Refusal on his part led to her urging him. He would then display outbursts of temper and for the rest of the day would be unwilling to do anything she asked of him. The teasing by the boys led to feelings of a lump in the throat which was present even as he spoke about it to the examiner. During the past year he had developed a twitch in the left eye which recurred mostly when he was excited or ashamed. His sleep was not disturbed but he frequently dreamed that he was a great athlete.

Physically he disclosed a normal height of 61.8 in. but a weight of 140.5 lb. which was some 30 lb. heavier than the maximum normal for that height. He showed a eunuchoid skeletal disproportion, the upper measurement being 29.0 and the lower 32.8 in. The obesity was of the shoulder and pelvic-girdle type; there was a genu valgum. The penis was 1.5 cm. in length. Both testes were palpable in the scrotum but were about the size of a small almond. A sparse crines pubis had begun to appear. The results of laboratory studies were essentially normal, except that the B.M.R. was −10. Psychiatric survey disclosed only a keen sensitivity to his abnormal configuration and hypogenitalism, with mild reactions of depression, sulking, crying spells and temper tantrums. Psychometric study revealed identical mental and chronological ages.

Treatment consisted of explaining to the parents the origin of the child's bashfulness and obstinacy; the establishment in them of a more sympathetic attitude toward the child's disability and a recognition of his need for privacy during the early stages of treatment.

Discussions were held with the boy concerning the importance of maintaining social contacts; the differences existing between people generally were also stressed.

Injections of testosterone propionate, 10 mg. twice weekly, for 3 months led to a penile growth to 5 cm. (fig. 4) and a bodily configuration which took on a more normal appearance. The patient's entire attitude then changed. His personality again became characterized by the sociability which he had previously displayed.

Case 9, B.B., was 12 years and 1 month old, a boy with Fröhlich bodily configuration and a penis of 1 cm. length. When at home he constantly demanded attention, insisted on being bathed by his mother and pouted at any disappointment, regardless of its triviality. He preferred to remain alone and rarely if ever joined the games of other children of his age. The mental age was 10 years and 6 months and the I.Q. was 87; B.M.R. was −10.

He was treated with testosterone propionate, 25 mg. twice weekly, for one month; 10 mg. twice weekly for the next 2 months; and 5 mg. once weekly for the following month. Thyroid, 1 grain 3 times a day was also given and dietary restriction was instituted because of the low B.M.R. and obesity. In addition, he was encouraged to work toward a goal of greater self-dependence.

By the end of 4 months the penis had become 5 cm. in length, a small crines made its appearance and there was sufficient loss in body weight to alter the entire bodily configuration. Behavior at home was described as greatly improved. He developed the ability to care for himself, began playing with boys of his own age and really took pride in his newly developed maturity.

Case 10, H.A., a white male, 13 years of age, was referred by his family physician because he was fat, had genital infantilism and was moody. By moody was meant that he periodically became quiet, sullen, irritable when spoken to, preoccupied and frequently stared into space. Physically he was of normal height, 60 in. but weighed 183 lb., at least 80 lb. overweight, and disclosed a typical Fröhlich bodily configuration. The penis was so small that it could not be seen when he stood straight. The scrotum appeared bi-partite, resembling labia majora. The crines was present but was of the feminine type. The left testis was felt in the scrotum and appeared to be about the size of a pea. The right testis was smaller and was situated near the external ring. The findings in neurological examination were negative. Psychiatric survey disclosed an appreciation of being different and the admission of frequently having his feelings hurt because the other boys teased him. His sullen periods were taken up with thoughts about being different from other boys. This awareness made him feel sorry for himself, and a lump would form in his throat. At these times, if the matter were discussed he would become angry. Psychometrically he disclosed a mental age of 15 years and an I.Q. of 115. B.M.R. was −15; no other laboratory abnormalities were observed.

Treatment consisted of discussions in which explanations of biological variations were stressed in an attempt to create an attitude of acceptance. Encouragement was given concerning future possibilities of development. A work-play program was arranged in which activities with other children would be supervised in a gymnasium. The parents were advised to refrain from discussing his moodiness with him. They were merely to report it. A restricted diet and thyroid extract 1 grain, 3 times a day were prescribed and testosterone propionate 25 mg. 3 times weekly was given by subcutaneous injection. After 2 months this dosage was decreased to 25 mg. twice weekly. One month later, 3 months after treatment had begun he still weighed 165 lb. but the genital organs had developed so well that the penis was now 6 cm. in length and both testes had grown to normal size. As genital development improved the entire behavior of the child changed. Preoccupation ceased, he became highly spirited and he had become well adjusted in the group.

Five additional patients, all presenting behavior problems of one kind or another were also found to present varying degrees of genital infantilism. These, too, responded in similar satisfactory fashion. Psychotherapy in all cases consisted of attempts to establish

acceptance at least temporarily, and afford encouragement. A brief report of these cases follows:

Case 11, H.F., 15 years old, began showing signs of irritability 2 months prior to his first visit and wanted to stop school. His marks had been good but now he said he could not concentrate. The boys omitted him from their games because he was slow. Physically he showed an obesity (weight 164 lb.) but was of normal stature (60 in.). The genitals were undersized; the penis was 3 cm. long and the testes were descended but small. Testosterone propionate, 25 mg. twice weekly, for 3 months led to normal genital development. Dietary restriction resulted in loss of weight to 140 lb. With bodily change came improvement in emotional responses and a renewed interest in school.

Case 12, G.E., 16 years and 4 months of age, displayed crying spells and loss of appetite for the past 6 months. Examination disclosed a normal height of 63 in. and weight of 110 lb. but small genitalia, although a crines was making its appearance. His friends who were now maturing were teasing him. He tried to avoid them. Psychometry disclosed a mental age of 15 years, 2 months. Testosterone propionate, 25 mg. twice weekly for 4 months resulted in a growth of genitalia so that the penis increased from its original length of 4 cm. to 8 cm. At the end of 4 months he began to masturbate. Examination of the ejaculate disclosed living spermatozoa. His spirits in the meantime had undergone a remarkable improvement. The problems of masturbation and venereal disease were taken up with him and he was discharged.

Case 13, T.Y., 12 years of age, had for the past year been impudent to his parents. Before this time he had been well behaved. Neither threats, punishment, nor reasoning had any effect on the boy. Examination disclosed mild obesity but normal physical measurements otherwise. The genitalia were small, the penis 2.5 cm. in length, the testes descended but pea-like in size. No basis for his misbehavior could be determined. Testosterone propionate, 25 mg. twice weekly for 2 months, followed by 10 mg. doses twice weekly for 2 more months resulted in penile growth to 5 cm. and testicular development to normal size. With genital development the child's behavior improved.

Case 14, J.S., a 17-year-old high school student, began staying away from gym class without satisfactory reason. His parents also stated that he spoke of quitting school although he had always gotten along quite well before. Examination disclosed normally descended and fairly well developed testes but a penis 4 cm. in length. In discussion he explained his recent behavior as arising from his desire to keep his knowledge to himself. A note was written to the principal asking that the temporary absence from gym class be excused. Testosterone propionate, 25 mg. 3 times weekly by subcutaneous injection, resulted in a penile growth to 7 cm. in 3 months. He then returned to gym class and has been getting along very well since.

Case 15, M.M., 17 years of age, began having attacks of paroxysmal tachycardia and complaints of weakness and nausea for several months. Cardiologic studies disclosed no evidence of cardiopathy but small genitals were discovered and he was referred for treatment.

No psychogenic factors could be elicited. He was treated with testosterone propionate, 25 mg. twice weekly by subcutaneous injection, and within 4 months the penis had grown from an initial 4 cm. to 7 cm. From the time the penis began showing signs of growth, *i.e.*, after the third injection, the weakness gradually improved and nausea disappeared. Since the second month of treatment there have been no tachycardial attacks

DISCUSSION

The series of cases herein studied emphasizes how closely the misbehavior of this group of problem children depended upon their endocrinopathically determined somatic defects. In such patients the evidence of somatic abnormalities may be rather general as exemplified by the presence of a Fröhlich bodily configuration or a eunuchoid skeletal disproportion. Frequently, however, such gross evidence of constitutional dysplasia may be entirely absent. Nor is the presence of infantile genitalia always the criterion of hypogenitalism, since in at least two of these patients the phallic development, while somewhat undersized would, under ordinary circumstances, be considered normal on routine physical examination. Such patients may well be classed as cases of masked hypogonadism.

That gonadal deficiency in laboratory animals frequently results in behavioral changes particularly involving sexual aggressiveness is quite well known (10). Such effects have been observed not only in castrated males who frequently fail to respond to the estrual female but also in spayed females who then become devoid of the cyclic receptivity, estrual courtship, peculiar vocalizations and posturings of the intact animal. The use of sex hormones experimentally has also emphasized the effect of the endocrines on such behavior. For example, testosterone propionate, the hormone used in our own studies, when administered to the newly hatched male chick or to the hen leads to premature cock-like reactions in the one (11) and to distinct masculine behavior in the other (12). When injected into castrated male guinea-pigs (13) or impotent male rats (14) the waning sex drive and capacity for copulation are again restored. That the response to this hormone is not always fixed is indicated by the female mating behavior displayed by male lizards (15) and some male albino rats (16) following such treatment.

In the human being, however, because of the increased complexity of personality structure and because of the tremendous influence of social and other experiential factors on personality development, endocrine defects, even when limited to the gonads, may influence behavior in other than mere sexual spheres. That anxiety, depression, and emotional instability

frequently accompany diminished sex drive, whether organically or psychically determined, are well known. And that these behavioral difficulties may be favorably influenced by adequate treatment with testosterone propionate has also been reported (17). In the series of cases herein studied it appears that the most frequent and probably basic cause for behavioral aberration, which in many instances not only upset the individual but also caused him to become a social problem, was an inadequate adjustment to the feeling of being different. Being different to the child usually implies being inferior. He therefore becomes inhibited, with the result that normal drives and otherwise outward expressions which ordinarily lead to the usual satisfactions of successful living, become restrained. Conflicts then arise only to be followed by circumvented types of response *i.e.*, problem behavior. The influence of inner conflict as a genetic dynamic factor in conduct disorders has long been known (18). It is the inadequate adjustment to being different that gives rise to the difficulty and not merely the actuality of being different. In the treatment of patients with non-alterable physical defects this principle becomes an important guide.

It is interesting to observe that the manner in which the child will react to his deficiency is unpredictable. It has been stated (19) that the child of the Lorraine-Levy hypopituitary type shows an 'aggressive-dominant' personality while the child with the Fröhlich configuration tends to be 'submissive-compliant.' On the basis of personal observation it appears that such personality relationships are not really fixed. As a matter of fact the personality reaction seems to depend largely upon the life's experiences of the individual. In the series of patients herein reported both aggressive and regressive personality types are to be found among the boys with Fröhlich configuration. It does appear, however, that the patient with retarded mentality is more apt to be retiring than the one with a higher level of intelligence who more frequently becomes overly-aggressive. But each case must be approached individually and psychotherapy must be utilized in accordance with the patient's needs. For the most part this consists of re-education, the use of a well planned routine best adapted to the needs of the patient, and the correction of irritating influences in the home situation.

The use of specific hormone therapy is extremely important since only in this way is it possible to alter those original somatic defects which initiated the difficulty. The use of testosterone propionate in these cases, because it so rapidly developed the genitals to a more normal size, may, therefore, be considered to have had a profound therapeutic effect. The dosage of this hormone, like that of other endocrine preparations, must be graded in accordance with the degree of structural deficiency. In well-marked hypogonadism a dosage of 25 mg., 3 times weekly appears to be satisfactory. This dosage can then be decreased both in amount and frequency as improvement occurs. It is interesting to note that in a number of patients this hormone not only led to phallic growth but in several instances also resulted in the descent of previously undescended testes and even to testicular growth.

This latter observation is particularly noteworthy since testosterone propionate has been described as causing structural testicular defects in the rat (20, 21) and depression of testicular function as judged by decreased sperm output in the human being (22, 23). From personal experience, both experimentally and clinically (24, 25), it may be said that if testosterone propionate is observed to produce deleterious effects on the testis, it probably indicates that too much of the hormone has been used in that particular individual. This opinion is based not only on the experimental observation that suitably small, although still androgenically potent, dosages failed to depress the testis (26) but also on the fact that the testis of the normal adolescent boy continues to grow in spite of the secretion of progressively higher concentrations of androgens (27).

Finally, it is important to emphasize the complexity of the problem which embraces the endocrinopathic child who misbehaves. Fortunately, the patients reported in this communication responded well. Others, less fortunate however, failed to alter their behavioral tendencies in spite of improvement in their physical defects (28). In these it appears that a basic psychopathic propensity was so deep-rooted constitutionally that they lacked that plasticity which must be present if there is to be benefit from psychotherapy.

SUMMARY

Children with defective personality reactions frequently display endocrinopathic somatic defects. In a group of 15 such boys the behavior difficulties were found to be directly related to the frank or masked hypogonadism. Treatment with testosterone propionate, usually commencing with 25 mg., 2 or 3 times weekly, led to phallic growth in all cases. In several patients with undescended testes, testicular descent and growth also resulted. Concomitant psychotherapy was also used. This consisted of discussions with a view toward re-education, the establishment of a planned routine to include supervised activities in a group, and the restoration of more healthy home situations.

All of the patients responded by establishing more satisfactory attitudes toward their defects and all developed a more acceptable behavior. The complexity of the problem is emphasized, however, by calling attention to other dysplastically constituted behav-

ior-problem children who failed to improve in their behavior even after the physical defects had been corrected.

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Pubertas Precox in A Six-Year-Old Boy Produced by a Tumor of the Testis, Probably of Interstitial Cell Origin

[Neoplastic Hypergenitalism]

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GONADAL HYPERFUNCTION may be divided into two general types, *a*), primary and *b*), secondary. There has been some doubt that such an entity as primary hypergonadism exists, provided the gonads are situated normally, especially with our newer knowledge of the essentiality of the anterior pituitary gonadotropic hormone or hormones for gonadal development and function. However, this conception does not take into consideration the possibility of tumors, interstitial cell or adrenocortical, the secretions of which may have androgenic activity.

Pubertas precox may be due to four known factors, *a*), anterior pituitary hyperfunction, *b*), pineal disturbance, *c*), certain adrenal cortex tumors or disturbances and *d*), interstitial cell tumor of the testis.

There are frequent instances of precocious puberty produced by anterior pituitary gonadotropic hormones, especially in girls, as evidenced by secondary sexual development, early epiphyseal closure and onset of menstruation. Werner (1) cited two cases in which menstruation began at 1 and 7 years, respectively, with no other evident glandular imbalance and with normal hypophyseal fossae.

There has been some controversy (1) as to whether hypofunction or hyperfunction of the pineal gland may cause precocious puberty. Precocious puberty has been found accompanying certain teratomas of the pineal gland (2). It would seem logical that if the pineal is capable of influencing secondary sexual development abnormally, it would be due to hyperfunction.

Between the seminiferous tubules of the testes, in the loose connective tissue supporting them, there are clumps of cells known as interstitial cells or cells of Leydig, also spoken of as the interstitial glands. These interstitial cells are the source of the internal secretion, testosterone, which is responsible for the development of the male secondary sex characteristics and sexual instinct. Normally, these cells do not function sufficiently to cause secondary sexual development until the time of puberty when they are stimulated to activity by the anterior pituitary gonadotropic hormone. Interstitial cells are much more sparse in the testes of children than in adults. Stewart (3) states 'In old individuals, especially if the seminiferous tubules are atrophic, the interstitial cells may be notably increased. An increase in their number has frequently been observed in atrophic testes, especially in undescended testes; the seminiferous tubules are atrophic and the interstitial cells are prominent. Apparently the interstitial cells may increase when for any reason the seminiferous tubules fail to develop or become atrophic; but such hyperplasia does not occur in cases of orchitis with destruction of the tubules from inflammatory overgrowth of the intertubular connective tissue.'

Interstitial cell tumors cause less apparent disturbance in adults than in children because the secondary sexual characteristics are developed, but the tumors have the same histological picture.

Interstitial cell tumors in adults have been described by Kaufman (4), Stoppato (5), and Villata (6).

Sacchi (7) reported pubertas precox in a boy 9 years of age who had an alveolar carcinoma of the left testis. Stewart, Bell and Roehlke (3) reported the case of a 5-year-old child who had an interstitial-cell tumor of the right testis with the sexual phenomena characteristic for puberty.

Rowlands and Nicholson (8) published the report of a boy who, at the age of 6 years, began to show

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progressive evidences of precocious sexual development. At the age of 9 years the left testis, which was enlarged, was removed and an interstitial cell tumor was proved microscopically.

CASE REPORT

Our patient, when first observed, was 6 years and 9 months of age. He was a first child, born at full term and the delivery was normal. His weight at birth was 8.75 pounds. The first teeth erupted at 6 months; he talked and walked at one year and was continent at 15 months, all of which are within normal developmental limits. He is in the second grade at school, learns well, makes good grades and his social contact has been normal until recently.

Fig. 1. Patient, aged 6 years and 9 months. Note marked secondary sexual, skeletal and somatic development.

About 15 months ago, when he was 5.5 years of age, his mother first noticed abnormal hair growth about the external genitals, which were larger than normal at that time. The external genitals continued to increase in size (fig. 1) and he had frequent erections. The hair growth about the genitals became more marked and hair began to grow in the axillae, on the lips, chin and face. He was taller than normal for his age, the bodily configuration was heavier and the muscles in general were prominent and firm. The facial features became of the late adolescent type and during the past month the voice had become deeper in tone and had more volume.

About two months before observation by one of us (A. A. W.) he was found in a garage caressing a 6-year-old girl. This alarmed his mother and caused her to seek advice.

An interesting bit of information was obtained from the mother. Since he was two years of age he has smoked as many as 50 cigars without becoming ill. These were given to him by people other than his mother who, when she knew of it, would forbid his smoking.

Personal history. He sleeps soundly, his appetite is very good and he drinks no coffee or tea. He has had measles and mumps; no operations. The father and mother are living and well and he is the only child.

Physical examination. His height is 53.75 inches; the normal height for his age is 45 to 48 inches; his weight is 73.75 pounds, the normal being 42 to 52 pounds. The upper measurement is 26.25, the lower 27.5 inches and one-half span is 26.25 inches. The hands are very broad and the fingers are relatively short. The body is warm and the skin has normal moisture. The boy is large and has general skeletal development characteristic for a boy from 10 to 12 years of age. The muscles are overdeveloped for his age and are firm. The hair of the scalp is heavy and coarse. There is increased hair growth on the upper lip.

The penis, when flaccid, is 3.75 inches long and 1.5 inches in diameter, with glans in proportion. The left testicle is about 8 mm. in diameter and 1 cm. long. The right testicle is the size of a medium-sized olive. Both testicles show increased firmness. There is marked hair growth over the scrotum and pubis. The inguinal and femoral lymphatic glands are palpable, moderately enlarged and firm. The prostate is palpable, shows moderate development and the consistency is soft. All of the deciduous teeth are present, except the two lower central incisors which are permanent teeth; they are only partially erupted. The thyroid is about normal in size. Examination of the lungs and heart is negative; the pulse is 80, the blood pressure is 110 mm. Hg systolic and 70 diastolic. There is no abdominal dullness over the back, in the lower thoracic or upper lumbar regions or in the abdomen which might be suggestive of adrenal tumor. The kidneys are not palpable.

Laboratory findings. Blood studies showed Hb., 84 per cent; red cells, 4,200,000; white cells, 7150; differential count, juvenile 3, stabs 10, segmented 68, lymphocytes, 20; monocytes, 1 to 2; blood group, 4; results of the Kahn test, negative; non-protein nitrogen, 27 mg. per cent; blood sugar, 100 mg. per cent; chlorides, 512 mg. per cent; diastase 98 units (normal range 80 to 150); calcium 11.1 mg. per cent; total protein, 7.4 gm. per cent; albumin, 4.8 gm. per cent; globulin, 2.6 gm. per cent; serum inorganic phosphorus 9.6 mg. per cent (normal for children, 4–6); phosphates, 5.2 Bodansky units (normal 5 to 12 units); cholesterol, 162 mg. per cent. Results of sugar tolerance test in mg. per cent: fasting, 72; one hour, 125; 2 hours, 108; 3 hours, 80; 4 hours, 72.

The Friedman test of the urine for gonadotropins was negative. Basal metabolic rate was −14 and −15 per cent.

Roentgenograms show markedly advanced bone development. There are no abnormal shadows over the renal

or adrenal regions and the kidney pelves shadows are normal.

It was suspected that there was a tumor of the right testis (Vitt). This gonad was removed Feb. 13, 1942.

Pathologist's report. The specimen consisted of a testis measuring 2.5 by 1.5 cm. Near one pole could be felt a nodule of firmer consistency than the surrounding tissue. Section through the long axis of the testis showed this firm area to be a yellowish gray tumor, of roughly oval shape and measuring 12 mm. in maximum diameter (fig. 2). The small tumor was situated just beneath the capsule of the testis, and protruded inward in such a fashion as to displace a considerable portion of the testicular tissue. The tumor nodule was quite circumscribed and appeared sharply separable from the testicular tissue.

Microscopically, the tumor consisted of rather dense masses and columns of cells separated by a thin, scanty connective tissue stroma. In some areas thin elongated columns of cells formed the predominant arrangement, and produced an appearance suggestive of the columns of the adrenal cortex. In other areas there were small rounded, oval, or irregular groups of cells separated by the thin stroma. The individual cells were of oval or polyhedral shape, usually with prominent cell boundaries and abundant faintly eosinophilic granular cytoplasm. The nuclei were oval, slightly eccentric, and often contained a single prominent nucleolus. The cells were all similar, showing but little variation in size, shape or staining properties. Some cells were large due to abundant cytoplasm, but the nuclei showed no variation, and mitoses were not seen. Staining by Sudan III and osmic acid revealed no stainable lipoid content of the tumor cells. Near the periphery of the tumor a few atrophic testicular tubules were surrounded by tumor cells but, for the most part, the tumor was sharply separated from adjacent testicular tissue by a thin connective tissue band (fig. 3 and 4).

The tumor tissue in its microscopic appearance was rather strongly reminiscent of the adrenal cortex because of the columnar arrangement, which was prominent in some areas, and because of the abundant, slightly granular cytoplasm of the individual cells. However, the cells had a morphology similar to the interstitial cells of the testis. The interpretation of the nature and origin of the tumor cells would seem to be that they were either adrenal cortical tissue or interstitial cells of the testis. The histological appearance was similar to that of the interstitial cell tumor of the testis reported by Stewart, Bell and Roelhke (3). Through the courtesy of Dr. M. K. Shimken, sections of the tumor were compared with those of interstitial cell tumors of the testis induced in mice by injec-

Fig. 2. Tumor of the testis removed from patient, aged 6 years and 9 months.

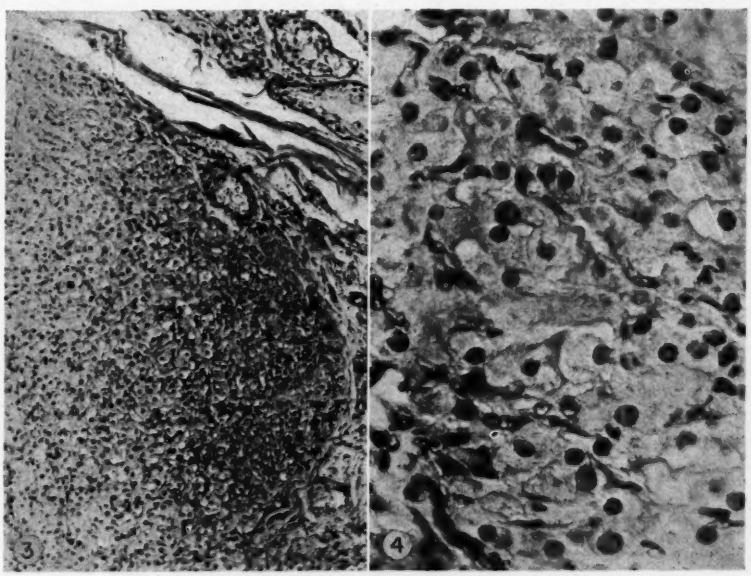

Fig. 3. Low power photomicrograph of the tumor of testis. Fig. 4. High power photomicrograph of the tumor showing cells resembling interstitial cells.

tion of stilbestrol. They were found to be closely similar. The weight of evidence suggests that the probable diagnosis is interstitial cell tumor of the testis.

On June 1, 1942, (3.5 months after operation) an examination of the boy showed the facial expression to be more child-like, the coarse hair on the upper lip has disappeared, there is less genital hair growth, the penis is about the same length but the glans seems smaller. The left testicle has increased in size to that of a medium-sized olive and has normal consistency. The voice has not returned to normal pitch. His mother states that 'his aggressive attitude has changed to gentleness and he wants to be around his mother. Formerly he wanted to be with adults and did not want to play with children of his own age; now he shuns adults and seeks the companionship of children.'

In the past 8 months he has grown 1.75 inches and his weight has increased 5 pounds.

SUMMARY

Hypergenitalism was first noticed in a boy at 5.5 years of age, when the mother found abnormal hair growth about the external genitals, which were larger than normal at that time. At 6 years, 9 months, of age the external genitals were adult in size, there was marked genital and pubic hair growth, with moderate hair growth on the upper lip, chin, face and in the axillae. The voice was deep in tone, and of considerable volume; the facial features were adolescent in type. He was at least 6 inches taller and 20 pounds heavier than normal for his age. The muscles were overdeveloped and firm. He sought the company of adults, and libido had been manifested. Roentgenograms showed markedly advanced bone development. The right testis, including the tumor, was surgically removed. The pathological interpretation is that the tumor was either *a*), derived from an adrenal rest in the testis, or *b*), that it was an interstitial cell tumor, the weight of evidence being strongly in favor of the latter.

Three and one-half months after the operation there was evidence of regression of the abnormally developed secondary sexual characteristics.

CONCLUSIONS

1. A study of this patient suggests strongly that the secretion of the interstitial cells of the testis may cause development of secondary sexual characteristics in the male.

2. This study also presents further evidence that the secretion of the interstitial cells may accelerate skeletal and somatic growth and development.

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Comparative Values of Chorionic Gonadotropic Hormone and Testosterone Propionate in Treatment of Cryptorchidism and Hypogenitalism

[Treatment of Cryptorchidism]

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THE PRESENT COMMUNICATION is based upon the results obtained by the administration of chorionic gonadotropic hormone alone or in alternation with male sex hormone in twenty-five boys and one adult with cryptorchidism and hypogenitalism. The cases are subdivided as *a*), those of cryptorchidism in which chorionic gonadotropic hormone alone was administered; *b*), those with cryptorchidism in which male sex hormone was administered in alternation with chorionic gonadotropic hormone, either after the unsuccessful use of the latter or without previous treatment and *c*), cases of hypogenitalism treated with one or both of the hormones.

All of the patients were studied in accordance with the methods and procedures described in previous communications. These include a complete physical examination, roentgenographic studies of the sella turcica and of the wrists, basal metabolic tests, specific dynamic action and blood chemistry studies (1). The effect on the cryptorchidism and on the external genitalia will be discussed in the present report, while that on the height, growth and bone development is considered in a separate communication. All cases of cryptorchidism in this series are of the true type. Testes of the receding type or those which could be forced into the scrotum by either manipulation or heat are considered as instances of pseudo-cryptorchidism and are not included.

Group 1. This group consists of 18 boys with cryptorchidism, ranging in age from 5.5 to 14.5 years. The condition occurred in boys who were otherwise normal in 7 instances, in 10 boys with adiposogenital dystrophy and in one with adiposogenital dystrophy and eunuchoidism. There were 10 cases of unilateral involvement and 8 of bilateral; the undescended testis was in the abdomen in 4 of the bilateral and in 5 of the unilateral cases and in the inguinal canal in the same distribution. The condition of the external genitalia was as follows: Normal, 2 cases, both with unilateral cryptorchidism; underdeveloped, 14 cases (8 with bilateral and 6 with unilateral cryptorchidism); and overdeveloped, two cases, both with unilateral cryptorchidism.

The treatment in this group consisted of the intramuscular injection of chorionic gonadotropic hormone[1] in doses of from 250 to 500 R.U. twice a week. This was changed to an equivalent number of I.U. after the introduction of the latter standard. The dosage ranged from a minimum of 3000 to a maximum of 20,000 I.U., with an average of 8650 I.U. in the successful cases (those with complete descent of the testes); and a range of 15,800 to 64,000 I.U. with an average of 39,480 I.U. in the unsuccessful cases. The duration of treatment varied from 2 to 9.5 months, with an average of 4.5 in the successful cases; from 5 to 22 months in the unsuccessful with an average of 12.5 months. Treatment was continuous for about 3 months, discontinued for one or two months and then resumed, if necessary. Supplementary treatment was given as indicated; boys with adiposogenital dystrophy received an appropriate diet high in proteins and low in carbohydrates and fats, with adequate supply of vitamins and oral administration of desiccated thyroid and anterior pituitary substances.

In evaluating the results, a testis was considered to be completely descended when it entered into the scrotum and remained there. Descent as far as the external ring or to the upper border of the scrotum

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[1] The chorionic gonadotropic hormones were supplied as *a*), Pregnyl, Roche-Organon, Inc., Nutley, N. J., *b*), Follutein, E. R. Squibb and Son, New Brunswick, N. J., and *c*), A. P. L. Ayerst, McKenna and Harrison, Rouses Point, N. Y.

was listed as partial descent. In a few instances the testis descended into the scrotum and then retracted, but eventually remained in the scrotum after further treatment. In these cases, the latter date was considered as that of complete descent.

Treatment of cryptorchidism by chorionic gonadotropic hormone in this group resulted in complete descent in 45 per cent, partial descent in 33 and none in 22 per cent. The response was better in the inguinal type of cryptorchidism. Irrespective of location, better results were obtained in bilateral than in unilateral involvement, as gauged by the incidence of complete descent. Partial descent, however, resulted more frequently in the unilateral type.

TABLE 1. EFFECTS OF CHORIONIC GONADOTROPIC HORMONE ON CRYPTORCHIDISM

Types of Cryptorchidism	Total Number	Complete Descent		Partial Descent		No Descent	
		No.	%	No.	%	No.	%
Unilateral	10	3	30	5	50	2	20
Bilateral	8	5	62.5	1	12.5	2	25
Abdominal	9	3	33.3	3	33.3	3	33.3
Inguinal	9	5	56	3	33	1	11
Total	18	8	45	6	33	4	22
Associated conditions							
A. Normal boys							
unilateral	5	0	0	3	60	2	40
bilateral	2	1	50	1	50	0	0
	7	1	14	4	57	2	29
B. Boys with adiposogenital dystrophy and							
unilateral	4	3	75	1	25	0	0
bilateral	6	4	66.6	0	0	2	33.3
eunuchoidism and unilateral	1	0	0	1	100	0	0
	11	7	64	2	18	2	18

Total failure was observed in two cases of unilateral cryptorchidism in normal boys with a definite history of mechanical obstruction due to previous operations, and in two instances of bilateral cryptorchidism with adiposogenital dystrophy.

This is too small a series upon which to base definite conclusions, but a comparison between the results in the apparently normal boys and in those with adiposogenital dystrophy supports our contention that supplementary treatment is necessary and is beneficial in the endocrine type of cryptorchidism. Complete descent was obtained in the boys with adiposogenital dystrophy in 64 per cent, partial descent in 18 per cent and a failure of descent in 18 per cent of the cases. Complete descent occurred in 14 per cent, partial in 57 per cent and none in 29 per cent in the normal boys. If we exclude the two cases of failure due to mechanical causes, in which medical treatment could never be of benefit, the percentage of complete descent in the normal group is still lower (40 per cent) than in the endocrine group.

The best response to treatment with chorionic gonadotropic hormone was obtained in the 9 to 11-year age group, excluding the isolated case of a 5.5-year-old boy.

Group 2. This group consists of 6 patients with cryptorchidism, 5 from 9 to 15 years of age and one adult of 30 years. The boys had had previous treatment with various preparations of chorionic gonadotropic hormone; 3 of them had been treated intensively by us. There were 3 instances of bilateral abdominal cryptorchidism and 3 with unilateral inguinal involvement. Three of the boys had had an initial adiposogenital dystrophy which had improved under treatment, 2 were normal boys and the adult presented the obese type of eunuchodism with unilateral cryptorchidism.

Testosterone propionate[2] was administered twice a week in strengths of 5 to 10 mg. and further dosage was adjusted to the individual requirements and response. An increase to 25 mg. twice a week was considered necessary in 3 of the older boys. The adult received 25 mg. 3 times a week from the beginning of treatment. Testosterone propionate was continued for 4 to 8 weeks and then discontinued and chorionic gonadotropic hormone administered from 1 to 3 months. This alternation was adhered to for the entire period of treatment except for intervals lasting from several weeks to several months.

The dose of the chorionic gonadotropin averaged 12,425 R.U. The duration of treatment varied from 2 to 9 months with an average of 5.5. The adult received a total of 1750 mg. of testosterone propionate, as a result of which partial descent occurred; 5000 I.U. of chorionic gonadotropic hormone produced complete descent. None of the boys showed any response in the descent of the cryptorchid. A partial response was observed in the adult after 3 months of administration of testosterone propionate, as evidenced by a descent of an abdominal cryptorchid into the lower third of the inguinal canal and into the upper part of the scrotum, but with retraction. Administration of 1000 I.U. of chorionic gonadotropic hormone twice a week was followed by ultimate descent into the scrotum.

Group 3. There were 20 patients with underdeveloped genitalia. Three of these were boys who presented a clinical picture of adiposogenital dystrophy and eunuchoidism. One was a boy of 10 years and 11

[2] The testosterone propionate was supplied by Roche-Organon, Inc., Nutley, N. J., as Neo-Hombreol, and as Oreton by Schering Corp., Bloomfield, N. J.

months with primary eunuchoidism and giantism, one was an adult, 30 years of age, who showed the obese type of eunuchoidism and unilateral cryptorchidism; 15 were boys with various grades of hypogenitalism. The penis ranged in size from that of infantile to somewhat less than normal for the age. The scrotum varied from a flat scrotum with no pouch to one of fairly normal size and appearance. The testes were descended in 5 cases and undescended in 15; in the former cases practically all of the testes were smaller than normal but none was atrophied. The three components of the external genitalia, penis, scrotum and testes, showed the same tendency to underdevelopment, but in a number of instances the scrotum was normal and the testes hypoplastic, and vice versa.

Chorionic gonadotropic hormone was administered to 19 boys and in alternation with testosterone propionate to 10 patients. In the cases with associated cryptorchidism, treatment was continued after descent of the testes had been obtained in order to further stimulate the testicular function.

The effects of treatment upon hypogenitalism and hypogonadism were evidenced by increase in the size of the external genitalia, appearance of secondary sex characteristics and by psychological changes. The younger boys showed a favorable response in the size of the penis, scrotum and descended testes and at times by the premature appearance of pubic hair and turgescence of the scrotum. In the older boys there ensued the development of pubic, axillary, and, later, of facial hair, deepening of the voice, enlargement of the penis, testes and scrotum, turgescence of the scrotum, occasional priapism and nocturnal emissions. The effects on the size of the penis, scrotum and testes were not always parallel, that is, for example, growth of the penis was not always

Table 2. Effects of alternating administration of chorionic gonadotropic hormone on cryptorchidism

Age Group	Total Number	Complete Descent	Partial Descent	No Descent
Boys	5	0	0	5
Adult	1	1		

accompanied by enlargement of the scrotum and testes. In practically every one of the older boys with bilateral cryptorchidism in whom treatment was unsuccessful, there was enlargement of the phallus and scrotum, and the appearance of pubic hair, in spite of nondescent of the testes. Acne appeared in a few boys. A more aggressive attitude in general, and an awakening interest in girls were noted in some of the older boys. The eunuchoid adult in addition to the changes described above, experienced libido and a change in his psychological attitude. In the boys with adiposogenital dystrophy there was a marked change in body contour with a reversion to the male type of build with a loss of adiposity in general, especially in the mammary, abdominal and trochanteric regions.

The successive treatment with testosterone propionate and chorionic gondaotropic hormone was more effective in correcting genital hypoplasia and developing secondary sex characteristics than chorionic gonadotropic hormone alone. Of those patients

Table 3. Effect of treatment of cryptorchidism at different ages

Age Group, Years	Total Number	Complete Descent		Partial Descent		No Descent	
		No.	%	No.	%	No.	%
5-5	1	1	100				
8 to 9.	5	1	20	2	40	2	40
9 to 11	7	4	57	3	43	0	0
11 to 14.5	5	2	40	1	20	2	20

treated with the latter, the penis attained normal proportions and appearance in 8 cases; it became slightly overdeveloped in 2 and remained underdeveloped in 9. The use of combined treatment in the latter 9 patients was followed by an increase in size and development of the penis in 3 cases, the development of normal proportions in 5 and persistent underdevelopment in one. The testes in all of the successful cases were normal or slightly enlarged and never atrophied.

The average dosage of the chorionic gonadotropin for the group was 21,788 R.U. over a period of 9.5 months; that of testosterone propionate was 320 mg. over 4.5 months.

DISCUSSION

Cryptorchidism is being treated currently either by endocrine therapy or by surgical procedure or by combination of both. The endocrine agents which are being used are chorionic gonadotropic hormone from pregnancy urine, chorionic gonadotropic hormone from pregnant mare serum, gonadotropic hormone from the anterior pituitary lobe and synthetic male sex hormone, testosterone propionate.

Our studies confirm those of others that chorionic gonadotropic hormone from pregnancy urine is the most efficient type of therapy, but the degree of efficiency is still a debatable subject. Successful outcome, that is, complete descent of the testes into the scrotum, is obtained, on the average, in from 30 to 50 per cent of the cases, ranging from enthusiastic reports of 73 per cent (2–5) to pessimistic results of 20 per cent (6). Our present results of 45 per cent success is midway between these figures. None of the usual arguments against the higher figures is applicable in our study, as we meticulously excluded all in-

stances of possible pseudocryptorchidism. All cases in which the testis was at the external ring or at the upper border of the scrotum at the completion of the study were considered as instances of partial descent.

No definite statement can be made as to the number of units of chorionic gonadotropin required, but the initial dosage should not be less than 250 I.U., 2 to 3 times a week, to be increased to 500 I.U. at weekly intervals. In persistent cases, it may be necessary to increase the dosage to 750 or 1000 I.U. twice a week. If descent of the testes is not produced by 500 I.U. given 2 to 3 times a week over a period of several months, nothing is to be gained by giving larger doses except for the production of a further increase in the size of the external genitalia.

The results of treatment are more dependent upon the dosage than upon the duration, but treatment should be continued for at least 6 months, and even longer if necessary; it need not be interrupted because of formation of anti-hormone since these probably are not formed during long-continued treatment.

The results in this and our former series of study in boys with adiposogenital dystrophy, as compared with those in the apparently normal group, confirm our belief that cryptorchidism in many instances is a manifestation of thyroid and pituitary deficiency and that supplementary treatment is necessary and beneficial in this type (7). In hypothyroidism we recommend the additional administration of desiccated thyroid substance, and in adiposogenital dystrophy, desiccated thyroid and anterior pituitary substances orally and a fat-reducing diet.

Treatment may be effective at any age from 5 to 14 years. Spontaneous descent may occur in some uncomplicated cases between the ages of 10 to 16, but it is not desirable to postpone treatment until puberty in the hope that this will take place.

Failure of treatment may be due to mechanical obstruction, treatment instituted at too early an age, insufficient amount of gonadotropic hormone and continued endocrine imbalance.

Surgery is indicated in every case which has resisted hormonal treatment and in which failure is due to mechanical factors. No boy should be subjected to surgical intervention unless and until he has had intensive treatment with chorionic gonadotropic hormone by injection for at least 6 months. This therapy is beneficial even in cases due to mechanical obstruction as it produces an increase in the size of the testes, inguinal canal and scrotum and prepares the field for operation.

On the other hand, no boy who has failed to respond to medical treatment should be permitted to continue to adult life without correcting the cryptorchidism by operative means.

Irrespective of the surgical method employed, every operation for cryptorchidism should be preceded by treatment with gonadotropic hormone for no less than 6 months and this should be followed by endocrine treatment for another month or two. This procedure prepares the field prior to operation and later tends to prevent recession.

The literature on the effect of testosterone propionate upon cryptorchidism is scanty. Zelson and Steinitz (8) reviewed all the available reports from 1936 to 1938 and found that the injection of male sex hormone alone produced complete descent in 23.4 per cent of the cases of cryptorchidism and partial descent in 27.6 per cent. Cases of bilateral involvement were more amenable to treatment than were unilateral. They reported, in addition, complete descent in 15 per cent, and partial descent in 45 per cent of 17 boys treated by them. The dosage of testosterone propionate ranged from 5 to 10 mg. twice a week for a period of 4 to 10 weeks, with a total dosage of 60 to 180 mg. Four of the boys, in whom no descent had occurred, were then given a combination of testosterone propionate (5 mg.) and chorionic gonadotropic hormone (500 R.U.) 3 times a week for 3 to 6 weeks. Complete descent was obtained in two of these cases.

In a second report in 1940, Zelson and Steinitz (9) observed in 17 patients who were given a combination of testosterone propionate (5 mg.) and chorionic gonadotropic hormone (500 R.U.) that complete descent was obtained in 53 per cent at the end of 3 to 12 weeks of treatment. Four of these boys had been treated with both hormones alone or successively, without any effect. On the basis of their findings, they conclude that combined treatment with testosterone propionate and chorionic gonadotropic hormone is superior to that of either hormone alone or to successive treatment with both.

Sexton (10) reported complete descent within 16 to 20 weeks in 47 per cent of boys from 3 to 15 years of age, after treatment with chorionic gonadotropic hormone. At a subsequent date, he then administered testosterone propionate alone to 9 of these boys in dosages ranging from 5 to 75 mg. a week for periods of from 7 to 36 weeks. He observed no further descent of the cryptorchid in any of the patients. Turner (11) also has reported unsuccessful results in cryptorchidism with testosterone propionate administered alone or subsequent to therapy with chorionic gonadotropic hormone in 3 patients, one a 7-year-old boy and 2 eunuchoid adults. Our results confirm those of Sexton and Turner, in that we did not observe any effect on the undescended testes in 5 boys. We did, however, obtain partial descent in a eunuchoid adult.

Caution is necessary in the treatment with testosterone propionate, either alone or with chorionic

gonadotropic hormone. The former should not be administered to boys under 9 or 10 years of age. Prolonged treatment should not be advised except in cases of primary eunuchoidism, but small maintenance doses may be given for comparatively short intervals in milder grades of hypogonadism, perhaps in cryptorchidism and in selected cases of short stature. An average dose of 10 mg. twice a week for 1 to 3 months is sufficient to produce the desired therapeutic response without any untoward effects in most instances of hypogenitalism. These effects, consisting of excessive growth of the penis, premature appearance of secondary sex characteristics, priapism, emissions and stimulated sex interest, may be produced in a small number of cases but they can be controlled by adjustment of the dose to the individual needs of the patient. Some authors report premature closure of the epiphyses and impairment of growth but we have not observed either of these in our present series.

Treatment for cryptorchidism with chorionic gonadotropin should be instituted between the ages of 5 to 9 years and should not be delayed until after puberty in the hope of spontaneous descent.

SUMMARY AND CONCLUSIONS

Chorionic gonadotropic hormone was administered to 18 boys with true cryptorchidism with the following results. Complete descent occurred in 45 per cent; partial descent, 33 per cent and no descent in 22 per cent. Better response was obtained in the cases of bilateral and in the inguinal types of cryptorchidism.

Boys with adiposogenital dystrophy were given supplementary treatment of desiccated thyroid and anterior pituitary substances and a diet high in protein and low in fats and carbohydrates. Better results were obtained in this type of boy than in the apparently normal boy.

Testosterone propionate was administered subsequent to and in alternation with therapy with chorionic gonadotropic hormone to 5 boys with cryptorchidism and to one adult with unilateral cryptorchidism associated with the obese type of eunuchoidism. Three of these boys had had previous treatment with chorionic hormone without success. The alternating administration of both hormones did not produce any further descent of the testes in the boys. Testosterone propionate produced a partial descent of an abdominal cryptorchid in the eunuchoid adult and subsequent administration of chorionic gonadotropic hormone was followed by complete descent.

Chorionic gonadotropic hormone was given to 19 boys with hypogenitalism, in alternation with testosterone propionate to 9 boys in whom the first type of treatment was unsuccessful, and to one eunuchoid adult who had not received previous treatment.

We conclude that the administration of chorionic gonadotropic hormone is more effective in producing complete descent of undescended testes than is testosterone propionate alone, or in alternation with chorionic gonadotropin. Supplementary treatment is necessary and beneficial in the cryptorchid boy with an associated adiposogenital dystrophy or hypothyroidism.

Testosterone propionate alone or in alternation with chorionic gonadotropic hormone is more effective than the latter in the treatment of hypogenitalism.

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EDITORIALS

ENDOCRINOLOGY AND PSYCHOSOMATIC MEDICINE

THERE IS NOW apparent in the field of clinical medicine a strong trend toward the recognition of the part played by psychological factors in the causation of physical symptoms. Equally important is the relationship of physical factors in the genesis of 'psychological' disorders. So intimately related are the two categories of causes and of effects that their separation amounts, in principle, to a falsification of the issue—a recourse to dogmatic artificiality. In modern psychological and psychiatric circles the differentiation of psyche and soma has come to be recognized as a gratuitous over-simplification that cannot do justice to the essential facts. A sick man is a sick man whether his illness arises primarily in structural defects or in his life experiences. It is less than scientific to confine attention to either the somatic or the psychological facet of the total individual. The physician is doing less than his full duty to the patient when he fails to give his attention to the real etiology, whatever it may be, and to utilize appropriate therapeutic agencies of any legitimate sort whether drugs, hormones, physical therapy, re-education, or what not. Often a skilful combination of two or more therapeutic modalities leads to results better than can be obtained by any single method of treatment.

Endocrinologists, as a group, have tended to be somewhat reluctant to follow the leadership of sophisticated internists toward the goals of psychosomatic medicine. But perhaps the time has now come to give more attention to the man that has the glands rather than merely to the glands themselves and to the bodily effects of their perturbations.

Elsewhere in this issue appears an article by Rubenstein in which the eclectic approach is exemplified. A group of boys suffering from retarded genital development were studied with regard to the psychotraumatic results of their infirmity. Not only was androgen therapy prescribed but attempts were made to remove the scars of the personality by appropriate re-educational psychotherapy.

The field of endocrinology offers many opportunities for further studies of psychodynamics. In such studies the technical resources of trained psychologists are often needed for penetrating approaches to the problems but at this juncture even the elementary aspects of the subject offer possibilities for productive instigation.

R.G.H.

COMMUNICATIONS TO THE EDITORS

TO THE EDITOR:

SIR: It has come to my attention that there is now considerable confusion regarding the strength of "Hytakerol" which is the only source of Dihydrotachysterol available in this country. The matter is a rather important one since all the work on this product in this country, including several papers of my own, have been carried out on the assumption that there were 5 mg. per 1 cc. instead of 1.25 mg., as seems to be the case.

FULLER ALBRIGHT.

This letter was submitted to the Winthrop Chemical Company and the following was received.

TO THE EDITOR:

Thank you for calling to our attention the enclosed letter from Dr. Fuller Albright regarding an apparent discrepancy in labels of Hytakerol (our brand of dihydrotachysterol) of old and recent manufacture. Formerly the labels of Hytakerol in Oil bore the statement that 1 cc. contains 5 mg. of dihydrotachysterol, whereas on the revised labels it is stated that 1 cc. contains the equivalent of 1.25 mg. of crystalline dihydrotachysterol.

Although we greatly regret that the new labeling has been confusing, there has been no qualitative or quantitative change in the composition of the product. Therefore, the dosage expressed in terms of a number of drops or of cubic centimeters is unaltered, but references to dihydrotachysterol by weight (i.e., in milligrams) require proportionate adjustment.

When Hytakerol in Oil was first made available for clinical use, it was honestly believed by chemists well versed in the mysteries of the sterols that the active constituent contained only dihydrotachysterol with virtually no admixture of other sterols. As a result of painstaking experiments in the course of years, dihydrotachysterol in pure crystalline form was recently isolated in minute amounts. Careful comparative studies then led to the conclusion that our preparation of dihydrotachysterol contains other relatively inert sterols formed during the process of irradiation.

The accompanying sterols of dihydrotachysterol are relatively inert from the standpoint of influencing the blood calcium level. They might be removed, but only with great difficulty and at prohibitive cost. Because of this, there has been no change in the product, but only in the labeling.

The situation with reference to Hytakerol is not unique nor anomalous. For example, Viosterol in Oil contains irradiated ergosterol (standardized in terms of vitamin D units determined by biologic test), which is actually a mixture of sterols. On the other hand, Drisdol (our crystalline vitamin D_2) is a pure principle, produced at considerably higher—though not prohibitive—cost.

WINTHROP CHEMICAL COMPANY INC.
E. J. Foley, M.D.

170 Varick St.,
New York City

Abstracts of
CURRENT CLINICAL LITERATURE

Editor: DANIEL A. MCGINTY. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, J. P. PRATT, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, BORIS B. RUBENSTEIN, EMMERICH VON HAAM.

PARATHYROID

ANDERSEN, D. H. AND R. R. SCHLESINGER.

Renal hyperparathyroidism with calcification of the arteries in infancy. *Am. J. Dis. Child.* 63: 101. 1942.

Renal hyperparathyroidism is rare in infants. Two cases are described in infants aged 6 and 4 weeks in whom the outstanding symptoms were tetany, twitchings and convulsions.

High phosphorus and non-protein nitrogen and acidosis were associated with low serum calcium in one and with normal content in the other child. The renal insufficiency was not apparent at first and was manifested chiefly by consistently low specific gravity of urine. The appearance of calcified arteries in roentgenograms stimulated further investigation of the urinary tract and discovery of congenital anomalies. The osseous lesions were never conspicuous. The essential postmortem findings in both cases were: severe renal anomaly, parathyroid hypertrophy, metastatic calcification of middle-sized arteries throughout the body and osseous lesions similar to those found in osteitis fibrosa. The differences between the picture in infancy, childhood, adolescence and adult life are described.—*M.B.G.*

THYROID

LERMAN, JACOB and H. D. STEBBINS.

The pituitary type of myxedema. Further observations. *J. Am. Med. Assoc.* 119: 391. 1942.

The authors report an additional case of pituitary type of myxedema which when confirmed at autopsy was proven similar to the original case described by J. H. Means. Laboratory procedures indicated gonadal and adrenocortical hypofunction and absence of gonadotropic and diabetogenic substances of the pituitary.—*C.P.*

PONCHER, H. G., I. P. BRONSTEIN, H. W. WADE AND J. C. RICEWASSER.

Creatine metabolism in hypothyroid infants and children; further observations. *Am. J. Dis. Child.* 63: 270. 1942.

Determinations of the urinary output of creatine may serve as a valuable aid in the diagnosis of hypothyroidism, especially in infants and in older children when initial cholesterol levels are within normal limits and the osseous development is normal. At present biochemical and metabolic tests are not sufficient in themselves for the diagnosis of hypothyroidism or for the regulation of the dosage of thyroid.

The authors present a comprehensive discussion of the subject and describe the findings in six patients.—*M.B.G.*

PANCREAS

WAGNER, R., P. WHITE AND I. K. BOGAN.

Diabetic dwarfism. *Am. J. Dis. Child.* 63: 667. 1942.

From a comparison of 200 diabetics with 159 non-diabetic children, the following conclusions are drawn:

1. While over height is characteristic of juvenile diabetes, stunting of growth occurs in 5 to 10% of diabetic children.

2. The weight-height relationship is normal in diabetic children except in some girls who have a specific form of obesity.

3. The onset of the sexual development of the average diabetic child with normal height and weight tends to occur precociously but sexual development does not progress at the normal rate. Retardation of sexual development is present in nearly all retarded diabetic children and disturbance in the appearance of secondary sex characteristics is more frequent than in non-diabetic children.

4. Dental caries is less frequent in diabetic than in non-diabetic children, but pyorrhea is more frequent.

5. Enlargment of the liver is common in diabetic children and adolescents.

6. Dwarfism. The diabetic child is most susceptible to retardation in growth from the twelfth to sixteenth year of life and from the second to sixth year of diabetes. Retardation in most girls has an earlier onset than in boys. Sexual development is delayed in every patient with dwarfism at the time of maximal retardation in height. The onset of retardation in growth in most cases occurs during the period of sexual development. Retardation of bone development is generally present. Arteriosclerosis, general and in the eye, is found in 47% and in 28%, respectively, of retarded diabetic children.

The incidence of the various etiological groups, according to the authors' classification of diabetic dwarfism is as follows: hypopituitary-like dwarfism, 50%; transitory infantilism, 27%; constitutional type, 12%; undernutrition, 2.5%; congenital anomalies, 2%; neglect, 1% and tertiary syphilis, 1%.

The best therapeutic results are obtained by the injection of anterior pituitary extract containing the growth hormone, 3 cc. every second day with thyroid substance, 1 to 3 grains a day by mouth. The highest insulin over-body weight quotients were found in the children treated with anterior pituitary extract and then in the thyroid treated group.—*M.B.G.*